HOSPITAL LIBRARY

VOLUME 90 NUMBER 3

APR 23 1952

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

March, 1952

The Influence of Cortisone on Artificially Induced Peritoneal Exudates. M. M. Cummings, M. C. Drummond, M. Michael, Jr. and W. L. Bloom 185

Studies with the Millikan Oximeter at the Bedside of Patients with Cardiac and Pulmonary Disease. Raymond Penneys 192

Observations on the Use of Propylthiouracil in Hyperthyroidism with Especial Reference to Long Term Treatment. Elihu S. Wing, Jr. and Samuel P. Asper, Jr. 201

Studies on a Chemical Continuum. W. Mansfield Clark 228

Book Reviews 254

PUBLISHED MONTHLY
THE JOHNS HOPKINS PRESS, Baltimore-18, Maryland
Made in United States of America

Copyright, 1952, by The Johns Hopkins Press

BULLETIN OF
THE JOHNS HOPKINS HOSPITAL

MANAGING EDITOR, FREDERIK B. BANG

ASSOCIATE MANAGING EDITOR, CHARLES G. ZUBROD

EDITORIAL BOARD

E. Cowles Andrus **Kennneth C. Blanchard** **John Eager Howard**
Charles R. Austrian **Edward M. Hanrahan** **Arnold R. Rich**

All correspondence relating to the publication of papers should be addressed to The Editor, Bulletin of The Johns Hopkins Hospital, Baltimore-5, Md.

Books for review should be sent to The Editor at the above address.

Correspondence concerning business matters and all remittances should be sent to The Johns Hopkins Press, Baltimore-18, Maryland, U. S. A.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75.

New subscriptions and renewals are entered to begin with the first issue of the current year. Subscribers in the United States are hereby notified that missing numbers cannot be replaced unless notification of loss is received in this office within 1 month following publication of the missing number; foreign subscribers 6 months.

Subscriptions in the British Empire except Canada may be sent to: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, London, W.C. 2.

Manuscripts. Manuscripts should be typewritten, one side of page only, and double-spaced. Following the title should appear the author's name, department, and the university and/or hospital he represents. A list of references (bibliography) in numerical sequence should appear at the end of article. Preferred style for references is as follows: Author's last name, initials. Title of book or article, with first word and proper names capitalized only. Name of journal (abbreviate), date of publication, volume number: page number. The Bulletin is not responsible for loss of a manuscript in mail. Author should retain a duplicate copy.

Illustrations and Tables. Legends are required for Figures and descriptive headings for Tables. Use Arabic numerals to number Figures (Fig. 1); use Roman numerals to number Plates and Tables (Plate I). It should be indicated exactly where Figures and Tables are to appear in text; Plates all appear at end of article. All Figures should be drafted in black India ink for 50% reduction to 4½ inch width. Glossy photographs must be supplied for all Plates. Original illustrations will be returned to author with galley proofs.

Reprints. Twenty-five reprints, without covers, are furnished gratis for each article. Additional reprints should be ordered when galley proofs are returned.

THE JOHNS HOPKINS PRESS

BALTIMORE-18, MARYLAND, U. S. A.

Entered as second class matter at the Baltimore, Md., Post Office. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

THE INFLUENCE OF CORTISONE ON ARTIFICIALLY INDUCED PERITONEAL EXUDATES*

MARTIN M. CUMMINGS, MARGARET C. DRUMMOND, MAX MICHAEL, JR., AND WALTER L. BLOOM

The Medical Research Laboratory, Veterans Administration Hospital, and the Departments of Medicine and Biochemistry, Emory University School of Medicine, Atlanta, Georgia

Received for publication September 13, 1951

Adrenal cortical hormones have been shown to produce changes in the lymphocyte (1, 2) and eosinophile (3) counts of certain animals and of man. It has been reported also that there is an increased migration of macrophages when exposed to certain of these adrenal hormones in tissue culture (4). Recently, it has been demonstrated that the functional activity of the macrophagic system can be altered by administration of adrenal cortical extracts (5). It was pointed out that, whereas adrenalectomy in rats results in a decrease in the number of Kupffer cells in the liver, whole adrenal cortical extract significantly increases the number of macrophages in the livers and spleens of these animals. The phagocytic activity of these cells was measured by administering thorium dioxide and determining the uptake of this material by chemical analysis of the tissues. It was postulated that adrenal cortical hormones stimulate the formation of active macrophages through a hypertrophy of fixed reticular or endothelial elements.

It has been demonstrated by Mudd, et al. (6) that physiological saline injected intraperitoneally into rabbits produces an exudate rich in polymorphonuclear leukocytes. Ponder and MacLeod (7) reported that the intraperitoneal injection of saline likewise produces a polymorphonuclear leukocyte increase in the circulating blood of rabbits. In previous studies we have shown (8) that there is a quantitative difference in the cellular response of the rat and the rabbit to the intraperitoneal injection of sterile mineral oil. The macrophage response of the rat to mineral oil stimulus was found to be significantly greater than that of the rabbit. The implications of this observation to the well known differences in the natural resistance of these species were discussed.

We thought it would be of interest to study the influence of cortisone on the cellular response to both saline and mineral oil which produce an inflammatory type reaction in the peritoneal cavity. It was also considered important to learn whether or not there were differences in the response of naturally re-

* Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

sistant and susceptible species of animals in an attempt to shed some light on the problem of host resistance to infection.

MATERIALS AND METHODS

Artificially induced peritoneal exudates were produced in rats and rabbits in response to the intraperitoneal injection of two different stimuli: (a) sterile mineral oil and (b) sterile physiological saline.

(a) *Oil-induced Exudates:* Peritoneal exudates were obtained 48 hours after the intraperitoneal injection of sterile mineral oil, in a manner previously described (8). Albino rats, weighing 160 gm. and albino rabbits, weighing 2000 gm., were injected subcutaneously with cortisone*. The rats received 5 mg. daily for 5 days and the rabbits 12.5 mg. daily for the same period of time. On the third day of cortisone administration, 25 ml. of sterile mineral oil per kilogram of body weight were injected intraperitoneally. Control animals which did not receive cortisone were also injected with mineral oil. Forty-eight hours later the animals were killed, and the peritoneal exudates were removed after agitation with a volume of heparinized Tyrode solution equal to the volume of instilled oil. Differential and white blood cell counts were made on the aqueous phase after separation of the oil layer in a separatory funnel.

(b) *Saline-induced Exudates:* Albino rats and rabbits, comparable in weight to those employed in the first part of the experiment, were injected intraperitoneally with 100 ml. of sterile physiological saline per kilogram of body weight, half of the animals having been treated with cortisone for 5 days as described above. After twenty-four hours the animals were sacrificed and the peritoneal contents transferred by pipetting to a flask containing heparin. The peritoneal cavities of some animals contained no fluid after this interval of time, and these were washed with 25 ml. of saline for the rabbits and 10 ml. for the rats in order to remove the leukocytes. Differential and total white blood cell counts were then performed.

RESULTS

Table I shows that the total peritoneal cellular response to mineral oil of the rats and rabbits was depressed by cortisone administration. It is interesting to note that the white cell counts of cortisone-treated rats were often depressed to the level of the control rabbits. These values are found to be highly significant when subjected to an analysis of variance.

Table II reveals that there is a reduction in the percentage of lymphocytes and polymorphonuclear leukocytes in the exudates of rats receiving cortisone. The mononuclear cells, however, were relatively increased. In the rabbits there was an increase in the percentage of polymorphonuclear leukocytes, but no significant change in the percentage of lymphocytes or percentage of mononuclear cells.

Table III shows that the depressing effect of cortisone on the cellular response of rats and rabbits to the intraperitoneal injection of sterile physiological saline is not very significant when subjected to a statistical analysis of

* Cortone acetate—Merck & Company.

TABLE I

Peritoneal Cellular Response to Mineral Oil of Rats and Rabbits as Influenced by Cortisone

EXP. NO.	NUMBER OF ANIMALS IN EACH GROUP	AVERAGE WBC/CU.MM.		AVERAGE LOGARITHM WBC	
		Control	Cortisone	Control	Cortisone
		Rats			
I	4	10880	6463*	4.0330	3.7687*
II	3	4441	725*	3.5603	2.6056*
III	4	5762	2812*	3.7325	3.3877*
IV	4	23800	6506*	4.2462	3.3877*
V	14	17285 ± S.D. 1870	10393 ± 2480	4.1857	3.9411†
		Rabbits			
I	3	483	275*	1.439	1.217*
II	4	981	169*	1.6200	1.0382*
III	3	1809	978*	1.1916	.623*
IV	4	4750	1156*	0.9892	.224*

* Analysis of variance of groups was carried out in both rabbit and rat experiments (Exp. I–IV). Common logarithms of the WBC were used in the analysis. In the rat experiment, F for difference due to treatment was 11.38 (d.f. 1 and 3), P = <0.05. In the rabbit experiment, F for difference in treatment was 115 (d.f. 1 and 3), P = <0.01.

† Analyzed by Fisher's formula for small series, P = <0.01.

TABLE II

Mean Differential White Cell Counts of Oil-Induced Peritoneal Exudates

GROUP	WBC/CU.MM.	SEGS	LYMPHS.	MONOS.
29 Control Rats	11320	40.5	27.8	31.7
29 Cortisone Rats	5536	29.8	16.7	53.0
14 Control Rabbits	1957	17.5	11.5	71.5
14 Cortisone Rabbits	645	26.1	13.0	64.0

TABLE III

Peritoneal Cellular Response of Rats and Rabbits to Intraperitoneal Saline as Influenced by Cortisone

EXP. NO.	NUMBER OF ANIMALS IN EACH GROUP	AVERAGE WBC/CU.MM.		AVERAGE LOGARITHM WBC	
		Control	Cortisone	Control	Cortisone
		Rats			
I	5	2650	2040	3.34644	3.29155
II	3	2200	2300	3.33705	3.35409
III	10	3755	2085	3.53157	3.28991
		Rabbits			
I	3	3517	2300	3.50627	3.38630
II	4	4400	2275	3.58839	3.27718
III	4	4312	1180	3.24207	2.09937

Analysis of variance of groups was carried out in both rabbit and rat experiments (I–III). Common logarithms of the WBC were used in the analysis. In the rat experiment, F for difference due to treatment was 3.4 (d.f. 1 and 2), P = 0.20. In the rabbit experiment, F for difference in the treatment was 2.0 (d.f. 1 and 2), P = 0.20.

TABLE IV

Mean Differential White Cell Counts of Saline-Induced Peritoneal Exudates

GROUP	WBC/CU.MM.	SEGS	LYMPHS.	MONOS.
18 Control Rats	2869	47.7	11.0	41.3
18 Cortisone Rats	2141	55.0	11.3	33.7
10 Control Rabbits	4078	70.7	3.3	29.0
10 Cortisone Rabbits	1585*	71.0	6.0	23.0

* Three rabbits with WBC below 200/cu.mm. are not included in the differential cell counts, because insufficient cells were available for reliable differentiations.

TABLE V

Phagocytosis of Oil Droplets by Cells Obtained from Rat Exudates

	PERCENTAGE OF MACROPHAGES PHAGOCYTIZING OIL DROPLETS	
Animals	Control Rats	Cortisone Treated Rats
Group I		
1	82	92
2	54	92
3	48	56
4	54	78
5	Not done	80
Mean	60	80
Group II		
1	76	20
2	18	88
3	44	66
4	50	60
5	64	66
Mean	50.4	60
Group III		
1	52	32
2	40	10
3	72	82
4	60	38
5	72	80
Mean	59.2	48.4
Mean of 3 groups	59.9	62.8

variance. This differs from the findings when mineral oil was used as a stimulus and suggests that normal saline does not serve as a strong excitant to call forth a cellular response.

Table IV reveals that cortisone produced no striking alteration in the differential cellular response of intraperitoneal saline in rats and rabbits. It is also interesting to note again the poor total white cell response in the peritoneal cavity of the rat when compared to the cellular response of this animal to intraperitoneal mineral oil injection (Table II).

There is some question whether the decrease in the white count of cortisone-treated animals was due to increased phagocytosis of oil droplets by macrophages. In order to elucidate this point a comparison was made of the number of oil droplets in the macrophages of the normal and cortisone treated animals. The results of this experiment are illustrated in Table V. A study of the oil

TABLE VI

Distribution of White Blood Cells in Aqueous and Oil Phases (in Vivo)

	WBC/CMM. IN NORMAL CONTROLS			WBC/CMM. IN CORTISONE TREATED RATS		
	Aqueous phase	Oil phase	Percentage in aqueous phase	Aqueous phase	Oil phase	Percentage in aqueous phase
Animal #1	8250	200		2650	400	
#2	12,400	25		1100	—	
#3	10,750	1350		4150	300	
#4	13,400	550		11,750	275	
#5	4700	25		5350	50	
Mean	9900	430	95.7%	5000	258	94.8%

TABLE VII

WBC Before and After in Vitro Exposure to Mineral Oil

	WBC/CMM. IN NORMAL CONTROLS (AQUEOUS LAYER) ADDED TO MINERAL OIL			WBC/CMM. IN CORTISONE TREATED GROUP (AQUEOUS LAYER) ADDED TO MINERAL OIL		
	Before rotation	After rotation 30 min.	Percentage decrease after rotation	Before rotation	After rotation 30 min.	Percentage decrease after rotation
Group of five pooled exudates	9500	6750	30%	2400	1600	33.3%

layer of the extracted peritoneal exudates show that there is no difference in the normal and cortisone treated groups (Table VI). When white cells from normal and cortisone treated animals were incubated at 37°C. with mineral oil and rotated for 30 minutes, there was an equal loss of cells in the normal and cortisone treated groups as shown in Table VII.

These results indicate that cortisone does not significantly alter the degree of phagocytosis of oil droplets and as a consequence the decrease in white counts observed in these animals is probably not the result of these cells being trapped in the oil layer.

DISCUSSION

The depression of the cellular response to a fixed stimulus by cortisone may be significant in altering the natural resistance of the host. Cellular response to an infection such as tuberculosis is orderly and usually results in localized lesions. Healing is manifested by formation of fibroblastic tissue around the local tubercle. This type of response is very striking in experimental tuberculosis in rats and other resistant hosts. In susceptible hosts there is also an orderly response to infection, but due to quantitative and qualitative deficiencies in factors of resistance, the end result is different, and death of the animal may occur.

Indices of cortisone action, such as decrease in spleen size, increase in glycogen content of the liver, and decrease in size of adrenals were usually present.

The lowering of the total white cell peritoneal response by cortisone suggests that acute inflammatory reactions are suppressed by this steroid. The significance of this depression of reaction to a stimulus such as mineral oil may explain in part why hosts ordinarily resistant to infection with tubercle bacilli develop fatal, progressive lesions when they receive this hormone (9–11).

SUMMARY

1. Cortisone administered to rats and rabbits depresses the total cellular response to the intraperitoneal injection of sterile mineral oil, but not to the injection of physiological saline.

ACKNOWLEDGMENT

The authors wish to acknowledge the work of Miss Nell Davis for her help in performing the cell counts.

BIBLIOGRAPHY

1. Dougherty, T. F. and White, A.: Functional Changes in Lymphoid Tissue Induced by Adrenal Cortical Secretion, Am. J. Anat., 1945, **77**, 81.
2. Dougherty, T. F., White, A., and Chase, J. H.: Relationship of the Effects of Adrenal Cortical Secretion on Lymphoid Tissue and on Antibody Titer, Proc. Soc. Exp. Biol. and Med., 1944, **56**, 28.
3. Hills, A. G., Forsham, P. H. and Finch, C. A.: Changes in Circulating Leukocytes Induced by the Administration of Pituitary Adreno-cortico-trophic Hormones (ACTH) in man, Blood, 1948, **3**, 755.
4. Heilman, D. H.: The Effect of 11-dihydro-17-OH-corticosterone and 11-dihydrocorticosterone on the Migration of Macrophages in Tissue Culture, Proc. Staff Meet., Mayo Clin., 1945, **20**, 318.
5. Gordon, A. S. and Katsh, G. F.: The Relation of Adrenal Cortex to the Structure and Phagocytic Activity of the Macrophage System, Ann. New York Acad. Sc., 1949, **52**, I.
6. Mudd, S., Lucke, G., McCutcheon, M. and Strumia, M.: On Mechanism of Opsonin and Bacterio-tropin Action; Correlation between Changes in Bacterial Surface Prop-

erties and in Phagocytosis Caused by Sera of Animals under Immunization, J. Exp. Med., 1929, **49,** 779.

7. Ponder, E. and MacLeod, J.: White Cell Morphology in Rabbits with Induced Peritoneal Exudates, J. Exp. Med., 1938, **67,** 839.
8. Bloom, W. L., Cummings, M. M., and Michael, M., Jr.: Macrophage Content of Oil-induced Peritoneal Exudates in Rats and Rabbits, Proc. Soc. Exp. Biol. and Med., 1950, **75,** 171.
9. Hart, P. D., and Rees, R. J.: Enhancing Effect of Cortisone on Tuberculosis in the Mouse, Lancet, 1950, CCLIV, 391.
10. Michael, M., Jr., Cummings, M. M. and Bloom, W. L.: Course of Experimental Tuberculosis in the Albino Rat as Influenced by Cortisone, Proc. Soc. Exp. Biol. and Med., 1950, **75,** 613.
11. Spain, D. M., and Molomut, N.: Effect of Cortisone on the Development of Tuberculous Lesions in Guinea Pigs and on their Modification by Streptomycin Therapy, Am. Rev. Tuberc., 1950, **62,** 337.

STUDIES WITH THE MILLIKAN OXIMETER AT THE BEDSIDE OF PATIENTS WITH CARDIAC AND PULMONARY DISEASE*

RAYMOND PENNEYS†

Departments of Preventive Medicine and Medicine (Physiological Division), Johns Hopkins University School of Medicine

Received for publication November 15, 1951

INTRODUCTION

The Millikan oximeter, an instrument which measures changes of the blood arterial oxygen saturation in the intact human ear, has been demonstrated to be of definite value in the study of hypoxemia (1, 2). It provides a measurement of the arterial blood oxygen saturation that is immediate, continuous and painless. This report describes an application of these features of the oximeter illustrating its usefulness at the bedside of patients with diseases of the heart and lungs in whom the detection, treatment and understanding of hypoxemia is of prime clinical importance. In particular, the value of the arterial saturation rise obtained with oxygen inhalation (3, 4, 5, 6) as an index of hypoxemia is further illustrated. Observations on the effect of some other procedures on the arterial oxygen saturation are also presented.

METHOD

The oximeter used was the Millikan automatically-compensated type (1). A storage battery was frequently used as a source of current. For convenience, the oximeter, a small oxygen tank, demand valve and necessary attachments were mounted on a small portable table (Figure 1) which could be transported quickly to the bedside of the patient. Oximeter "ear thickness" readings were always taken and were found not to affect the saturation readings appreciably (6). Brisk rubbing of the ear with the fingers was often done to hasten the "warming up" of the ear necessary before "saturation" readings could be made.

The patients studied were those with cardiac or pulmonary disease, or both, usually in whom the existence of hypoxemia was suspected clinically. A few patients with related conditions were included. None were suspected of having congenital heart disease. All were white adults. Twenty-seven patients were studied. Twenty-four of the patients were classified as "cardiac" or "pulmonary" when the disease was primarily either cardiac or pulmonary in origin or as "pulmono-cardiac" when both cardiac and pulmonary disease were believed to be present. Two other patients had polycythemia vera and a third was diagnosed as having "carbon monoxide intoxication".

---

* This investigation was done during the tenure of a United States Public Health Service Post-Doctorate Fellowship and was supported by funds made available for research in the Department of Preventive Medicine by Abbott Laboratory, Eli Lilly Co., Lederle Laboratory, Parke Davis and Co., Upjohn Co., The Ellis D. and Priscilla G. Slater Foundation and the United States Public Health Service.

† Present position, Instructor in Medicine, University of Pennsylvania School of Medicine.

When the saturation rise was used as a measurement of hypoxemia, the oxygen was delivered to the patient via a demand valve, an inspiratory-expiratory valve and a mouthpiece. The nose was obstructed by a clip. Oxygen was given for approximately 5 minutes or at least until the saturation reading of the oximeter no longer showed an increase. The severity of the patient's illness was assessed from his symptoms, physical examination and pertinent laboratory tests and correlated with the saturation rise.

Usually only one set of observations was made on one particular patient if the saturation rise with oxygen inhalation was not abnormally large, i.e. not greater than 6%. In those instances where the saturation rise was greater than 6%, oxygen was administered again after a change in the severity of the patient's disease had taken place. One patient (San, Figure 1), who had a normal rise when first studied, was given oxygen on several occasions as she went into and out of pulmonary edema.

FIG. 1

A few observations on the effect of aminophyllin, phlebotomy and thoracentesis on the arterial oxygen saturation were made when these procedures were being carried out for clinical purposes. Similarly, the demand valve was compared with other methods of administering oxygen where the patients were receiving oxygen for treatment of their disease. Another comparison, between the oximeter and Van Slyke-Neill blood gasometric method (2), was obtained where these latter analyses were made during the course of the patient's hospitalization.

OBSERVATIONS

The Rise of the Arterial Oxygen Saturation with Oxygen Inhalation in Relationship to the Severity of Disease. In Figure 2 the severity and the saturation

rise with oxygen inhalation are compared where the rise was measured more than once in any particular patient. A change in the severity of disease in any one patient was always associated with a corresponding change in the saturation rise. The more severe the symptoms such as dyspnea or orthopnea, the greater was the degree of hypoxemia. This is especially well illustrated by San, who was dyspneic and orthopneic the first time he was given oxygen by demand valve and showed a saturation increase of 4%. Several weeks later he suddenly developed pulmonary edema. Oxygen administration this time in-

FIG. 2. RISE OF THE ARTERIAL OXYGEN SATURATION, WITH INHALATION OF OXYGEN, AND THE SEVERITY OF DISEASE IN THE SAME PATIENT

Severity of disease is indicated as follows:

- in pulmonary edema.
- symptoms on complete bed rest.
- symptoms on slight exertion.
- symptoms on moderate exertion; ambulatory.
- asymptomatic with moderate exertion; able to carry on daily activities.

creased his saturation rise to 13%. He subsequently improved and his saturation rise with oxygen inhalation returned to 4%.

In Figure 3, all the measurements of the saturation rise made on the cardiac, pulmonary, and pulmono-cardiac patients are arranged so that patients with the same severity are compared in the three groups. For the same degree of severity, the pulmonary patients showed a greater rise than the cardiac, while the few patients with pulmono-cardiac disease showed the greatest rise. Only those cardiac patients who were severely ill, usually having pulmonary edema, showed an abnormally large rise with oxygen inhalation whereas pulmonary patients showed an equally large rise while still ambulatory and only slightly dyspneic. Again it can be seen that, in general, the more severe the illness, the greater was the rise of the arterial saturation with oxygen for each type of illness.

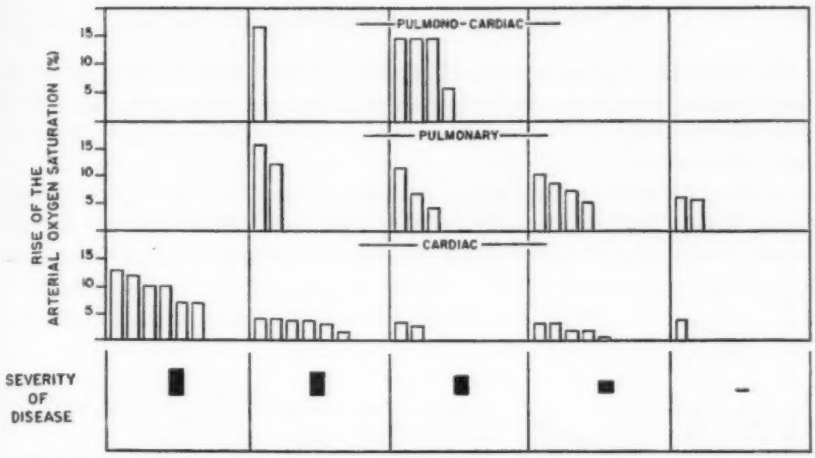


FIG. 3. RISE OF THE ARTERIAL OXYGEN SATURATION, WITH INHALATION OF OXYGEN, AND THE TYPE OF ILLNESS (CARDIAC, PULMONARY, OR PULMONO-CARDIAC).

Severity of disease indicated as in Figure 2.

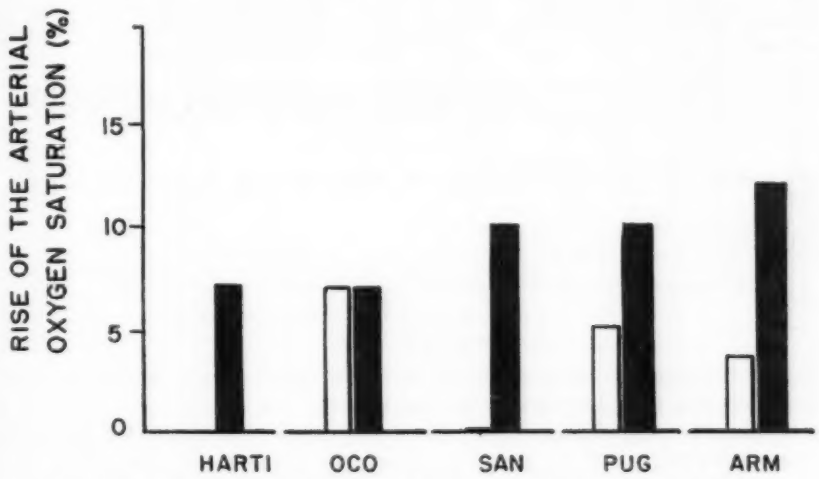


FIG. 4. THE RISE OF THE ARTERIAL OXYGEN SATURATION AND THE METHOD OF ADMINISTERING OXYGEN

□ indicates rise with tent, as in Oco and Pug, or with nasal catheter, as in Arm.

■ indicates rise with demand valve.

The rise is that observed over room air reading except with Harti who was *not* removed from tent before oxygen was given by the demand valve. San showed no rise when placed in the tent after breathing air.

One patient, not presented in Figure 3, in coma due to "carbon monoxide intoxication", was given oxygen by demand valve; a saturation rise of 11% was obtained. Two patients with polycythemia vera were given oxygen with saturation rises of 5 and 6%.

Method of Administering Oxygen. In Figure 4 the rise of the arterial oxygen saturation with the administration of oxygen by the demand valve is compared to that obtained by oxygen tent and oro-nasal catheter. Of the 5 pa-

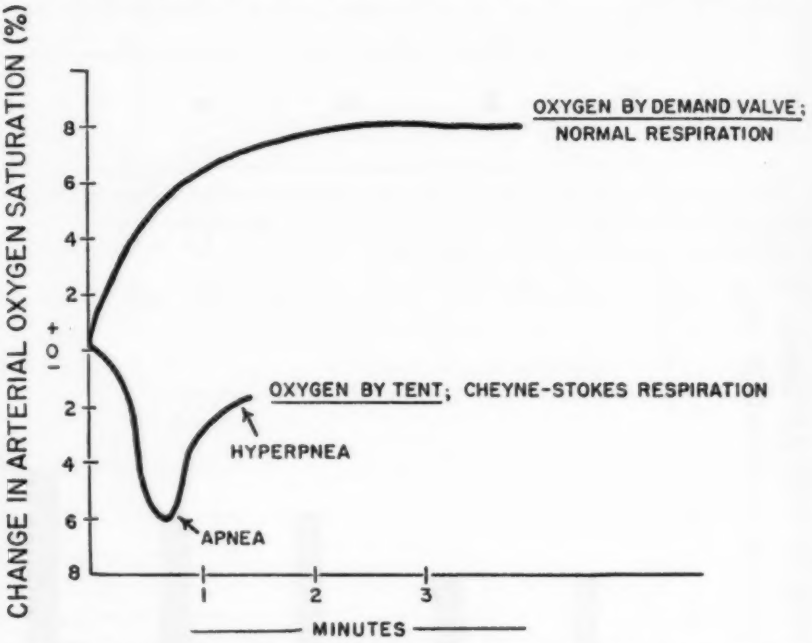


FIG. 5. CHANGES OF THE ARTERIAL OXYGEN SATURATION, AND RESPIRATION, IN A PATIENT (HARTI) WITH CHEYNE-STOKES RESPIRATION.

Saturation changes illustrated in the upper curve were obtained when additional oxygen was administered by demand valve while the patient remained in the oxygen tent.

tients on whom such comparative studies were made, 4 showed a greater rise of the arterial saturation with the demand valve. In one instance the saturation with demand valve increased 10% over that obtained with the oxygen tent. With 2 patients, San and Harti, the additional increase obtained by the demand valve produced further alleviation of respiratory distress. With the latter patient, the additional oxygen by demand valve promptly caused his Cheyne-Stokes respiration, with associated fluctuations of the arterial saturation, to disappear (Figure 5).

Effect of Other Clinical Procedures on the Arterial Oxygen Saturation. The oximeter was attached to one patient while a thoracentesis was being done, to another while he was having a phlebotomy or receiving aminophyllin and to two patients while they were being exercised. It was also attached to 3 orthopneic patients as their beds were being lowered. In no instance did any of these procedures result in a change of the arterial saturation. Observations were made for only short periods of time, however, not exceeding 15 minutes.

The administration of oxygen by demand valve, to these same patients, on the other hand, produced saturation rises from 3½ to 13%.

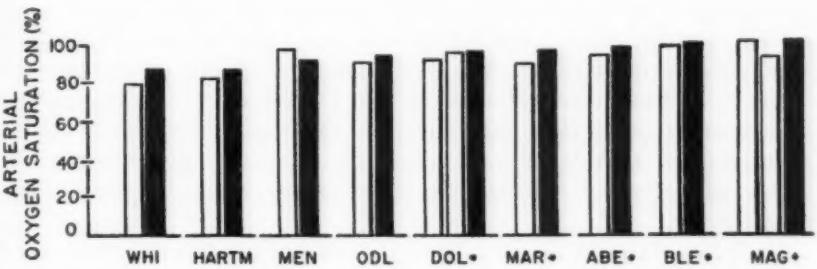


FIG. 6. COMPARISON OF THE ROOM AIR ARTERIAL OXYGEN SATURATION, AS MEASURED BY THE SATURATION RISE OF THE OXIMETER WITH OXYGEN INHALATION, AND BY BLOOD GAS ANALYSIS

■ indicates room air value obtained by the oximeter, assuming 100% saturation with oxygen inhalation.

□ indicates room air value obtained by blood gas analysis.

* indicates that readings were not made simultaneously.

The Arterial Oxygen Saturation While Breathing Room Air. The "room air" arterial oxygen saturation by oximeter and by Van Slyke-Neill analysis was available for comparison on 9 patients. In obtaining the room air saturation with the oximeter, the arterial saturation was assumed to be 100% with the inhalation of pure oxygen. The average value, breathing air, by oximeter was 92.3%, by Van Slyke, 90% (Figure 6). The two readings obtained usually agreed within 5%, the largest difference being 8.4%.

DISCUSSION

These observations made at the bedside of patients with cardiac and pulmonary disease further demonstrate the value of the Millikan oximeter in the study of hypoxemia. Although this instrument measures only relative changes

on the blood arterial oxygen saturation, our observations show that it can supply the following information which is of definite clinical value:

A. *The Arterial Saturation Increase with Inhalation of Oxygen*

Detection of Hypoxemia: Hypoxemia is frequently present in patients with congestive heart failure, bronchial asthma and related conditions, and is readily detected by the oximeter (4, Figure 2). A change in the severity of hypoxemia is correlated with a corresponding change in the severity of the disease in any particular patient (Figure 2). Daily measurement of the arterial saturation rise with the oximeter should therefore be of definite value in following objectively the patient's clinical course. Such studies should be of special value in following pulmonary or pulmono-cardiac patients in whom hypoxemia occurs relatively early in the disease (4, Figure 3). It should be borne in mind that certain diseases, such as the Tetralogy of Fallot, produce hypoxemia but do not allow full saturation of the arterial blood with inhalation of pure oxygen (4). Although a rise greater than 6% would indicate hypoxemia, a "normal" saturation rise would not in such instances rule out the presence of hypoxemia.

Evaluation of Oxygen Therapy: The value of the oximeter in determining the best method of administering oxygen (4) was again demonstrated. The importance of using the proper method of administering oxygen was well illustrated in our patient with Cheyne-Stokes respiration whose clinical picture was changed dramatically when additional oxygen was given by the demand valve. The oximeter, by determining the maximum possible increase of the arterial saturation obtainable with the inhalation of 100% oxygen, allows an *in vivo* measurement of the efficacy of oxygen therapy. This offers an advantage over the usual procedure of basing therapy on the oxygen concentration of the gas being administered. The portability of the oximeter, small oxygen tank, demand valve and necessary attachments (Figure 1) could make such studies routine in patients receiving oxygen therapy.

The use of the demand valve to administer oxygen in the detection of hypoxemia is also important since hypoxemic patients require high concentrations of oxygen to completely saturate their blood (4). Two of our patients exhibited a "normal" saturation rise when oxygen was given by tent, but showed an abnormally large rise when oxygen was given by demand valve (Figure 4).

Establishing a Clinical Diagnosis: Some types of polycythemia may be promptly differentiated from each other by measuring the arterial saturation rise with oxygen inhalation. "Primary" polycythemia, i.e. polycythemia vera, gives a normal rise since the arterial saturation of the blood while breathing air is normal (7). In contrast, "secondary" polycythemia associated with pulmonary disease will give a saturation rise greater than 6% if the blood is ab-

normally unsaturated while breathing air and becomes fully saturated with oxygen inhalation.

The unexpected detection of hypoxemia with e.g. "carbon monoxide intoxication" is of clinical importance by making one question the accuracy of his diagnosis.

B. *Detection of Rapid and Continuous Arterial Saturation Changes*

The advantage of having an instrument that allows instantaneous and continuous measurements is apparent in the detection of rapid saturation changes seen, for instance, in our patient with Cheyne-Stokes respiration. Studying the effect of phlebotomy, thoracentesis and intravenous medication on the blood arterial oxygen saturation by standard gasometric methods has been a difficult problem since continuous blood sampling and analysis is necessary for such information.

In conclusion, despite the limitations of the Millikan oximeter we have found it a simple and useful instrument for the detection, treatment and understanding of hypoxemia at the bedside of patients with cardiac or pulmonary disease. The oximeter should be of still greater value in patients who are more severely hypoxemic than ours, where rapid, painless and continuous measurements would be even more important.

SUMMARY

1. Studies with the Millikan oximeter were made at the bedside of 27 patients with cardiac and pulmonary disease.

2. Hypoxemia was detected by administering pure oxygen by demand valve and obtaining an arterial saturation rise greater than the normal of 6%. The severity of hypoxemia paralleled the severity of the disease in the same patient. The saturation rise with oxygen is suggested as an objective test of the clinical course of such patients.

3. For the same severity of disease, "pulmono-cardiac" patients were more unsaturated than "pulmonary"; the latter were in turn more unsaturated than the "cardiac" patients.

4. The importance of the use of the demand valve for oxygen administration in the detection and treatment of hypoxemia is demonstrated.

5. The saturation rise with oxygen inhalation was used to help differentiate similar clinical conditions from one another, e.g. polycythemia vera from secondary polycythemia associated with pulmonary disease.

6. The value of the oximeter in giving rapid and continuous measurements of the arterial saturation during Cheyne-Stokes respiration was demonstrated and its use during the administration of drugs, thoracentesis and phlebotomy is reported.

REFERENCES

1. Millikan, G. A.: The oximeter, an instrument for measuring continuously the oxygen saturation of arterial blood in man. Rev. Scient. Instruments, **13,** 434, 1942.
2. Comroe, J. H., Jr. and Wood, E. H.: Measurement of O_2 saturation of blood by filter photometers (Oximeters). Methods in Medical Research, **2,** 144. The Yearbook Publishers, Inc., Chicago, 1950.
3. Fowler, W. S. and Comroe, J. H., Jr.: Lung function studies. I. The rate of increase of arterial oxygen saturation during the inhalation of 100 per cent O_2. J. Clin. Invest. **27,** 327, 1948.
4. Godfrey, L., Pond, H. S. and Wood, F. C.: The Millikan oximeter in the recognition and treatment of anoxemia in clinical medicine. Am. J. Med. Sci. **216,** 605, 1948.
5. Douglas, J. C. and Edholm, O. G.: Measurement of saturation time and saturation tension with Millikan oximeter, in subjects with normal pulmonary function. J. Appl. Physiol. **2,** 307, 1949.
6. Penneys, R.: The correlation between the ear thickness and saturation readings of the Millikan oximeter. Bull. Johns Hopkins Hosp. **87,** 215, 1950.
7. Wasserman, L. R., Dobson, R. L., and Lawrence, J. H.: Blood oxygen studies in patients with polycythemia and in normal subjects. J. Clin. Invest. **28,** 60, 1949.

OBSERVATIONS ON THE USE OF PROPYLTHIOURACIL IN HYPERTHYROIDISM WITH ESPECIAL REFERENCE TO LONG TERM TREATMENT[1, 2]

ELIHU S. WING, JR.[3] AND SAMUEL P. ASPER, JR.

The Department of Medicine, The Johns Hopkins University School of Medicine, and the Thyroid Clinic of The Johns Hopkins Hospital

Received for publication December 19, 1951

In 1928 Chesney, Clawson and Webster (1) observed that cabbage induced goiter and hypometabolism when fed to rabbits. Subsequently, Mackenzie, Mackenzie and McCollum (2) noted that certain sulfonamides had similar properties in rats. While it is now known that the mechanism of goitrogenesis by cabbage is dissimilar from that by the sulfonamides (3), these and similar observations (4, 5) led Astwood to the development of thiourea and thiouracil (6) as agents for the treatment of hyperthyroidism. A number of clinical studies concerning the effectiveness (7, 8, 9, 10) and toxicity (11) of thiouracil were published. Structurally related, similarly acting compounds were also investigated (12, 13). It was soon apparent that thiouracil and related drugs were almost uniformly successful in ameliorating hyperthyroidism. However, propylthiouracil gained the widest acceptance due to its low toxicity.

Propylthiouracil has been extensively used in the preparation of hyperthyroid patients for subtotal thyroidectomy (14, 15, 16). Some investigators have been interested in the possible long term use of this antithyroid drug in producing remissions by medical means alone (17, 18). These studies have indicated that although the drug during its exhibition is effective in controlling hyperthyroidism, relapses to a hyperthyroid state after its discontinuance are frequent (19, 20). However, a sufficiently significant incidence of apparently permanent remissions after prolonged therapy has been reported (21, 22) to encourage further observations on the long term use of propylthiouracil. Little is known concerning the advisability of using propylthiouracil for protracted periods in the treatment of hyperthyroidism in a manner similar to the use of insulin in diabetes mellitus. This aspect of its usage awaits further study.

[1] Read in part before the Peripatetic Club, February 2, 1951, and The Johns Hopkins Medical Society, March 12, 1951, Baltimore, Maryland. A summary of this paper has previously appeared (cf. Proceedings of the Meeting of The Johns Hopkins Medical Society, Bull. Johns Hopkins Hosp. **88:** 562 (1951)).

[2] Expenses of these studies were in part defrayed by contracts between The Johns Hopkins University and the Office of Naval Research (1947–1948, 1949–1950) and the Atomic Energy Commission (1950–1951), and in part by the Maryland Division of the American Cancer Society (1950–1951).

[3] Department of Medicine Fellow, Private Out-Patient Service, 1950–1951.

During the past four years in the Thyroid Clinic of The Johns Hopkins Hospital,[4] two hundred and three hyperthyroid patients have been treated with propylthiouracil.[5] This report presents observations on the effectiveness of this treatment. Of these 203 patients, 44 were prepared for subtotal thyroidectomy with propylthiouracil, 34 failed to return after being on treatment for a few months, 11 were transferred to the care of private physicians, and the remaining 114 have been treated for varying periods with propylthiouracil. Eighty-seven of these 114 patients have been treated with propylthiouracil continuously for one year or longer and constitute "long term" cases. While data concerning the effective dosage, rate of response, toxicity, *etc.* have been collected from the entire series of 203 patients, the observations of general therapeutic effectiveness of propylthiouracil have been made only in the 87 long term patients.

SELECTION OF CASES AND METHOD OF STUDY

All patients seen in the Thyroid Clinic were in the low income group. Most patients lived in Baltimore. Family, social and financial stresses were common in these patients, factors possibly of importance in initiating and prolonging the disease.

A prearranged sorting system of the patients in this study was not used in testing the effectiveness of various therapeutic schemata. Therapy with propylthiouracil was instituted according to the general needs of each patient, limited only by our personal experience and available information of the drug's potentialities at the time of its administration. Accordingly, in the early stages of this study, the dosages tended to be small and patients were frequently prepared for surgery. During the past three years, however, dosages have been somewhat higher, and most patients have been maintained on propylthiouracil in the hope of inducing permanent medical remission. In a few instances strong solution of iodine (Lugol's solution) was used in conjunction with propylthiouracil. The results of this combined therapy are recorded only when differing significantly from those observed with propylthiouracil alone.

In all cases the diagnosis of hyperthyroidism was clearly established by clinical and laboratory evaluation. A complete history and physical examination were done at the patient's initial visit. On subsequent visits, observations concerning subjective and objective changes were made and recorded. Especially noted were the pulse rate, blood pressure, weight, prominence of the eyes as measured with the Hertel exophthalmometer, and changes in the goiter. An initial basal metabolic rate, serum cholesterol concentration, white blood cell count and hemoglobin were routinely obtained and repeated as indicated on subsequent visits. If the white blood count was less than 5,000 cells per $mm.^3$, the count was repeated and a differential study done. As a rule, patients were followed at biweekly intervals until a euthyroid status was realized. Thereafter, observations were made at bimonthly intervals.

---

[4] The Thyroid Clinic during the past four years has had the services of Drs. H. M. Thomas, Jr., E. V. Newman, J. H. Sisson, B. F. Jones, K. L. Zierler, B. P. Folk, J. Franklin, F. London, W. Arons, J. Colsky, N. S. Butterworth, H. M. Markley and the authors.

[5] Propylthiouracil (6-*n*-propyl-2-thiouracil) for this study was kindly supplied by Dr. Stanton M. Hardy of the Lederle Laboratories Division of the American Cyanamid Company, Pearl River, New York.

Unless medically contraindicated, patients were permitted to continue their usual activities during treatment.

The basal metabolic rate was occasionally not reliable, since extraneous factors often altered the determination in these outpatients. Clinical appraisal of a patient's status was considered the most accurate method of determining adequacy of response to treatment.

The initial total daily dosage of propylthiouracil was generally divided into three doses with oral administration at approximately eight hour intervals, since it has been shown that most of the drug is excreted within eight hours (23). Usually medication was taken on arising, at noon and on retiring; if this was inconvenient, it was taken after meals. The daily maintenance dose was usually given in equal parts at approximately 12 hour intervals. In instances in which the maintenance dose was small, it was given once daily.

Each physician followed his own patients whenever feasible, thus establishing continuity of treatment and encouragement of the patient's reliability, interest and faith toward the medical regimen.

DISTRIBUTION OF CASES

The sex, race and age distribution of these patients as well as classification of the goiters encountered is shown in Table 1. The usual predominance of this disease in women was noted, the ratio being 3.3 to 1. The age of the patients varied between 14 and 74 years, the majority (71.4%) being between 20 and 50 years of age. Hyperthyroidism was more common in women of all ages than in men. However, a greater incidence of the disease in men than in women over the age of 50 years was observed; 21 (44.7%) of the 47 males were over 50, while only 30 (19.2%) of 156 women were over 50 years of age.

The majority (77.8%) of the 203 patients had diffuse goiters, 13.3% had nodular goiters and 7.9% had recurrent hyperplasia of the thyroid gland after previous subtotal thyroidectomy. Two cases had coexistent hyperthyroidism and cancer of the thyroid gland, a higher incidence (1.0%) of this association than has been previously reported (24).

EFFECTIVE DOSAGE

The relative effectiveness of various initial dosages of propylthiouracil in 199 patients is recorded in Table 2. Response was considered satisfactory if a euthyroid state was achieved within 100 days following the commencement of therapy. With daily dosages of 150 mg. or less in 23 cases, only 12 (52%) responded satisfactorily. However, 108 (95%) of 114 patients responded adequately to 300 mg. daily. Since 300 mg. daily appeared to be highly effectual and was no more toxic than 100 mg. daily (*vide infra*), this dosage was adopted for most new cases. Similar observations on the effective initial dosage have been made by McCullagh, Hibbs and Schneider (25).

Of the patients failing to attain euthyroidism on the initial dosage, a few were prepared for subtotal thyroidectomy and the remainder received propylthiouracil in increased dosage. Of the six patients showing an inadequate response to the daily dosage of 300 mg., four subsequently responded to 400

TABLE 1

Sex, Race, Age and Type of Goiter in 203 Patients with Hyperthyroidism

AGE IN YEARS	MALE						FEMALE								TOTAL NUMBER OF PATIENTS
	White			Colored			White			Colored					
	Goiter*														
	D	N	R	D	N	R	D	N	R	D	N	R	C		
14–19	1	0	0	2	0	0	2	0	0	2	0	0	0		7
20–29	2	0	0	3	0	0	8	0	2	22	0	1	0		38
30–39	3	0	2	3	0	0	11	2	2	26	2	2	1		54
40–49	5	0	0	4	1	0	10	3	0	22	5	2	1		53
50–59	1	0	0	6	0	0	2	1	1	6	5	4	0		26
60–69	5	2	0	3	2	0	2	1	0	4	2	0	0		21
70–74	1	0	0	1	0	0	1	0	0	0	1	0	0		4
	18	2	2	22	3	0	36	7	5	82	15	9	2		
Total Number of Patients	22			25			48			108					
	47						156								203

Type of Gland

Diffuse	158 (77.8%)
Nodular	27 (13.3%)
Recurrent	16 (7.9%)
Cancer	2 (1.0%)

* D—diffuse; N—nodular; R—recurrent (after previous subtotal thyroidectomy) and C—cancer of thyroid.

TABLE 2

Effectiveness of Various Dosages of Propylthiouracil

DOSAGE	NO. CASES	EFFECTIVE IN	PER CENT EFFECTIVE
150 mg. (or less)	23	12	52%
200 mg.	26	15	58%
250 mg.	28	20	72%
300 mg.	114	108	95%
400 mg.	8	8	100%

The effectiveness of the initial daily dosage of propylthiouracil was observed in 199 patients, the drug being considered effective if euthyroidism was attained within 90 to 100 days. Four of the 203 patients of this study are not included since two developed urticaria after 14 days of treatment, and in two the initial therapy was methylthiouracil with later change to propylthiouracil for long term therapy.

mg., and two did not respond completely to doses as high as 500 mg. In some instances in which patients were unreliable in taking the dosage according to instructions control of the disease was unsatisfactory.

In patients attaining and maintaining euthyroidism, successive reductions in dosage were attempted to determine if euthyroidism would persist. If the initial dosage had been 300 mg. daily, it was reduced to 200 mg. If control of the disease was still evident after several months, the dosage was further reduced to 100 mg. In a few instances the dosage was then reduced to 50 mg. Consideration of discontinuance of therapy was not entertained unless the patient had successfully passed through these degradations of dosage.

RATE OF RESPONSE

Obvious individual variation in the rate of response to propylthiouracil therapy was apparent. Occasionally, especially in patients with milder disease, euthyroidism was gained within one month. In severer cases, control of the disease was not clinically manifest for as long as five months. In general, a period of approximately 90 to 100 days of continuous therapy was required before distinct euthyroidism was realized. While, on the average, control of the disease was well defined within 90 days, further symptomatic improvement was usually observed with prolongation of the treatment. For example, emotional readjustment and an improved state of psychobiologic well-being was in some instances only apparent after many months of continual therapy.

To confirm and elucidate the symptomatic improvement during therapy, ancillary evidence of the rate of response was gained by determining at various intervals the basal metabolic rate, body weight and concentration of cholesterol in the serum. These determinations approached normal at rates commensurate with the clinical response.

Basal Metabolic Rate: The average of serial determinations of basal metabolic rates, available in 78 of 87 cases treated continuously for at least one year, is shown in Figure 1, along with the average dosage of propylthiouracil. Approximately 90 to 100 days were required before the basal metabolic rate was within normal range. Indeed, this chart indicates that the average of the basal metabolic rates fell only to plus 15% normal standard. This is due, at least in part, to inclusion of 15 patients whose basal metabolic rates were never recorded as less than plus 20% normal standard even though they appeared euthyroid and, in part, to occasional unsatisfactory basal metabolic rate determinations on outpatients.

A comparison of the rate of response of patients receiving only propylthiouracil with those receiving propylthiouracil and strong solution of iodine revealed no essential difference. In patients pretreated with iodine some delay in response to propylthiouracil was occasionally noted; this phenomenon was originally observed by Astwood with thiouracil (9) and later with propylthiouracil (26).

Change in Weight: Weight loss of varying severity prior to treatment was noted in 74 (85%) of the 87 long term patients. During one year of continuous therapy, 69 of these 74 patients gained weight. In many instances weight gain

during treatment was so marked that dietary supervision was necessary. In the remaining five patients no weight gain or continued weight loss was observed during treatment; dietary restriction was at the physician's behest in these five patients because of the existence of contraindications to weight gain.

In the remaining 13 (15%) of the 87 patients, no weight loss was noted prior to treatment; indeed, in a few instances a slight gain in weight occurred during the onset of hyperthyroidism. Of these 13 patients, six demonstrated no significant weight change and seven gained weight during therapy.

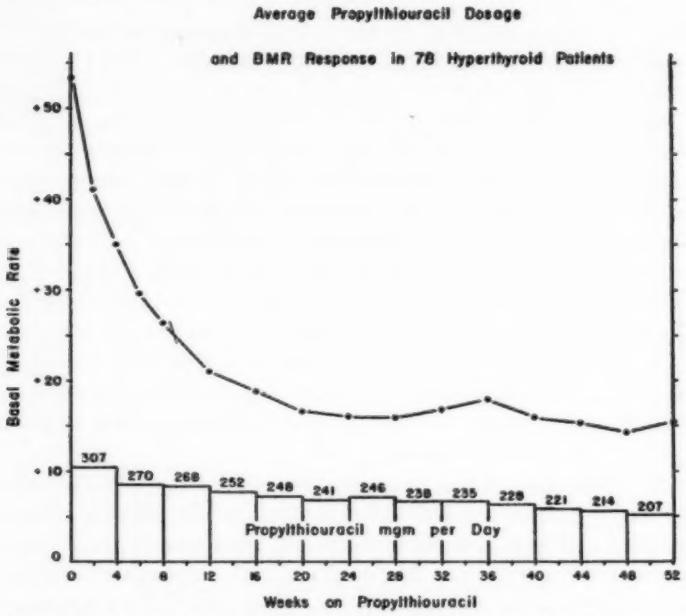


FIG. 1. The numbers above each block represent the average daily dosage of propylthiouracil in the 78 patients at the beginning of each consecutive 4 week period. The composite basal metabolic rate curve was obtained by charting the determinations in each of the 78 patients, interpolating to the points of time shown and averaging. The ordinate designates basal metabolic rate in percentage above the normal standard.

Change in weight during treatment was frequently used as an indication of response to therapy, especially in patients in whom weight loss was a prominent feature of the illness. In 35 patients whose weight loss exceeded 15 pounds (average 25.8 pounds) prior to treatment and who had frequent recordings of body weight during one year of continuous propylthiouracil therapy, a marked gain in weight was observed (Figure 2). After six months of therapy, approximately 70% of the loss had been regained, at 12 months almost 90%. This rate of recovery of body weight resembled a biologic growth curve.

Serum Cholesterol: It has been shown that the concentration of cholesterol in the serum is not a reliable diagnostic aid in untreated hyperthyroidism (27, 28), since the value usually is within the accepted limits of normal. However, Bartels (28) has demonstrated an increase of the serum cholesterol concentration during antithyroid therapy. In 48 long term patients of this series, the mean concentration of serum cholesterol prior to treatment was 183 mg.% (S.D.[6] = ±45 mg.%), a value in the lower range of normal in our laboratory. Thirty-eight (79%) of these patients had determinations of less than 200 mg.

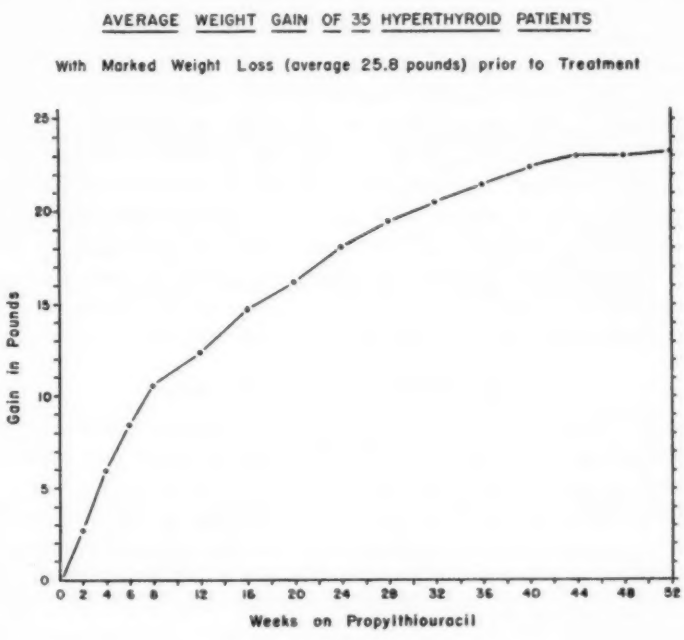

AVERAGE WEIGHT GAIN OF 35 HYPERTHYROID PATIENTS
With Marked Weight Loss (average 25.8 pounds) prior to Treatment
Gain in Pounds
0
5
10
15
20
25
0 2 4 6 8 12 16 20 24 28 32 36 40 44 48 52
Weeks on Propylthiouracil

FIG. 2

%. After one year of continuous treatment the mean value was 264 mg.% (S.D. = ±54 mg.%) with 44 (92%) of the patients having a value greater than 200 mg.%, again demonstrating that a rise in the concentration of serum cholesterol occurs during propylthiouracil therapy (Figure 3).

Further, as shown in Table 3, the most significant component of this rise occurred during the first two months of therapy, with only a small increment noted in the succeeding four months and little rise thereafter. After three years of continuous therapy, nine patients had a mean concentration of serum cholesterol of 282 mg.% (S.D. = ±42 mg.%). Thus, during the induction of

[6] Standard Deviation.

euthyroidism there is a distinct initial increase in the cholesterol concentration of the serum, whereas during maintenance therapy there is little further increase.

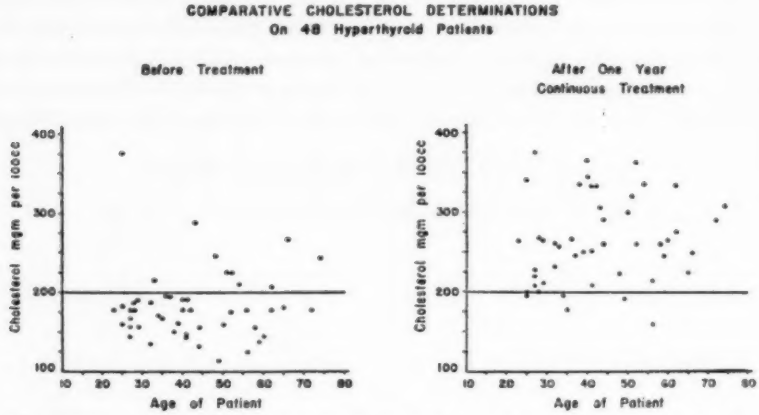


FIG. 3. The age of each patient in both charts is recorded as the age at the institution of treatment.

TABLE 3

Serum Cholesterol Before and During Therapy

	BEFORE THERAPY	MONTHS OF CONTINUOUS THERAPY		
		2	6	12
Cholesterol mg./100 cc.	182.7	245.8	262.2	264.4
% Increase		34.5	43.5	44.7

The values represent the average of the serum cholesterol determinations in 48 patients at the designated intervals. The serum cholesterol appears to rise sharply after initiation of treatment without further significant rise after 6 months of therapy.

ALTERATIONS IN THE SIZE OF THE THYROID GLAND

Enlargement of the thyroid gland was present in all patients prior to treatment, not infrequently being the chief complaint. In most instances the thyroid gland was considered on palpation to be two to three times normal size; occasionally it was four or five times enlarged. Thrills and bruits were encountered, especially in patients with large goiters and marked hyperthyroidism.

The size of the thyroid gland was frequently recorded in 81 of the 87 long term cases during prolonged therapy. Of these 81 patients, 65 had diffuse goiter, 8 nodular goiter and 8 recurrent hyperplasia after previous subtotal thyroidectomy. Forty-nine (60.5%) showed a definite decrease in the size of

the goiter during treatment, 28 (34.5%) experienced no change, and in four (5.0%) a definite increase in goiter size occurred. The greatest reductions in the size of the thyroid gland were observed in the 65 patients with diffuse goiter; in 21 of these patients the thyroid gland decreased to a barely palpable or impalpable state. Small to moderate sized goiters more frequently showed marked regression in size than larger diffuse goiters. Moreover, the vascular phenomena of thrills and bruits slowly regressed during therapy. In three of the eight patients with nodular goiter a distinct decrease in goiter size occurred during treatment.

In most instances in which the gland became smaller, no alteration occurred during the first few months of therapy; but as a euthyroid state developed and persisted, the gland began to decrease in size, and continued to decrease throughout months of treatment. Indeed, in several patients no change in goiter size was noted during two years of continuous therapy, and then over a period of a few months the thyroid gland decreased rapidly in size.

The four patients showing an increase in goiter size during prolonged therapy had diffuse goiters. In two patients the hyperthyroidism was poorly controlled even after increased dosage of propylthiouracil to 400 and 500 mg. daily. Enlargement of the goiter occurred in the other two patients when propylthiouracil dosage was decreased; yet euthyroidism was maintained.

ALTERATIONS IN EXOPHTHALMOS

Exophthalmos occurs in about 65% of patients with Graves' disease (29), and is rather unpredictable since it varies independently of the state of thyrotoxicosis (30). Progression of exophthalmos to a cosmetically undesirable or even a malignant stage is a serious complication in that no medical treatment is uniformly successful in ameliorating the exophthalmos.

Changes in the prominence of the eyes are significant only if recorded by an exophthalmometer (31), for, as Woods (32) has emphasized, apparent decrease of exophthalmos after successful treatment of the hyperthyroid state may be due to diminished stare and narrowing of the lid slits, while by measurement exophthalmos may have actually increased.

Of patients undergoing subtotal thyroidectomy for hyperthyroidism a subsequent increase of exophthalmos has been reported to occur in from 50 (31) to 65 (33) per cent, although progression to a malignant stage of exophthalmos is rare (34). A decrease of exophthalmos occurs in 10% (31) or less (33) of patients with Graves' disease treated surgically.

During thiourea or thiouracil therapy of hyperthyroidism little alteration of exophthalmos has been observed, with only an occasional instance of increase or decrease reported (9, 35, 36, 37, 38). Several investigators (18, 39, 40) have not observed exophthalmos to increase during propylthiouracil administration, yet Taylor, Large and Noth (41) noted that five of 22 patients with Graves'

disease had a marked increase of exophthalmos. The jeopardy of malignant exophthalmos developing following subtotal thyroidectomy in patients with hyperophthalmic Graves' disease (42) led Williams (18) to favor propylthiouracil for this variant of the disease.

In this study the prominence of the eyes was measured with a Hertel exophthalmometer. Readings of 17 mm. or more were considered to indicate abnormal orbital proptosis. An alteration of exophthalmos during treatment was deemed significant if it exceeded 2 mm. since the range of error in using the instrument is ± 1 mm. Exophthalmos was not observed in the patients with toxic nodular goiter. There were 52 patients with diffuse toxic goiter treated for one year or longer in whom exophthalmometric readings were made before and frequently during therapy; 39 had exophthalmos prior to treatment. Of the 52 patients, 28 (54%) had no change in the prominence of the eyes during treatment, 15 (29%) demonstrated a slight decrease of about 2 mm., and four (7.5%) showed a slight increase of about 2 mm. Decreases greater than 2 mm. were not observed. In five patients (10%), exophthalmic before therapy, an increase exceeding 2 mm. (4 to 7 mm.) was noted during treatment; none of these developed malignant exophthalmos.

Certain features of the five patients showing a significant increase in exophthalmos during treatment may be important. In four patients the hyperthyroidism was inadequately controlled because of insufficient dosage of propylthiouracil. Three patients received only 150 mg. propylthiouracil daily, one of whom also received strong solution of iodine. The fourth patient failed to take propylthiouracil as prescribed; an abstract follows:

H. B. (Unit No. 323648), a 27 year old colored female cook, had classic symptoms of Graves' disease of six months duration when she was begun on propylthiouracil, 400 mg. daily, in May, 1948. She responded satisfactorily, and the dose was reduced to 300 mg. daily. After approximately four and one-half months of treatment she voluntarily discontinued treatment for six weeks with prompt recurrence of symptoms. Propylthiouracil, 300 mg. daily, was reinstituted for one month, stopped for five weeks, started for another six months, and again discontinued for five weeks. Mild thyrotoxicity developed on each occasion that she withheld the drug. During the last four months exophthalmos increased three to four mm. in each eye. Because of her inconsistency in taking medication she was then given propylthiouracil for one month with strong solution of iodine added during the last six days, and a subtotal thyroidectomy was performed in September, 1949. The exophthalmos has not altered significantly since operation.

The fifth patient received both propylthiouracil and strong solution of iodine, the hyperthyroidism being adequately controlled. Six of the 52 patients received strong solution of iodine concomitantly with propylthiouracil, and it is perhaps significant that exophthalmos progressed in two of these.

Thus, in this small group of 52 patients with diffuse toxic goiter exophthalmos did not increase in those patients who responded satisfactorily and

were well controlled on propylthiouracil without iodine. Recently Thomas (43) has described a patient with hyperthyroidism who had an exacerbation of exophthalmos on each of two occasions that propylthiouracil therapy was withdrawn. Howard (44) has suggested that perhaps the intact thyroid gland, even though "propylthiouracilized", may possibly inactivate the exophthalmic component of the thyroid stimulating hormone. These results suggest that propylthiouracil therapy may be more advantageous in containing exophthalmos than the ablative forms of treatment of Graves' disease.

REMISSIONS AND RELAPSES

It is well recognized that if the period of administration of an antithyroid drug is less than 6 months in duration, relapse of hyperthyroidism is to be expected. Such has been the experience of Lahey (19), Bartels (15), Maddox (45), Taylor (41) and Pemberton, Haines and Keating (46), who stress the high incidence of relapse and, therefore, advise subtotal thyroidectomy with propylthiouracil as a preoperative adjunctive medication. Increasing evidence is arising that if continuous treatment of one year or longer is maintained, a significant incidence of apparently persistent remissions occurs. Williams and his coworkers (18) treated 111 cases of hyperthyroidism with antithyroid drugs including propylthiouracil and reported a 46% remission rate. However, Williams (21) later reported further recurrences of hyperthyroidism in this group of patients, thereby reducing the remission rate to 37%. Remission rates after long periods of propylthiouracil therapy have been variously reported as 33% by Kent, Shipley and Rundell (47), 50% by Seed, Linden and Lindsay (48), Cole (49) and Rowe (50), 64% by Greenberg and Bruger (39), and 80% by Beierwaltes and Sturgis (22, 51). Most of these investigators note that if relapse occurs, it usually does so within the first few months after cessation of therapy.

Of the 114 cases in this series being actively followed on a medical regimen, 66 (41.5%) have had therapy discontinued. Thirty-eight (57.5%) of these 66 cases had an exacerbation of hyperthyroidism following withdrawal of treatment (Figure 4). All the patients experiencing a relapse were again treated with propylthiouracil, and ten of these 38 cases had a second recurrence after stopping treatment. Thus, a total of 48 relapses occurred subsequent to cessation of propylthiouracil. Most relapses occurred promptly. Seventy-five per cent (36 cases) of the recurrences developed within 6 months after treatment was withdrawn and 95.8% (46 cases) within one year.

The ten patients having a second relapse did not take their medication regularly. In only two instances of the 20 relapses in these ten patients had the doctor authorized withdrawal of the medication. Nine of the patients had diffuse goiters and one nodular; all goiters were large or showed progressive enlargement throughout treatment. Four had persistent bruits. Three cases

had slight increase of exophthalmos and two had intermittent auricular fibrillation. Three patients who had progressively enlarging glands associated with persistent thrills and bruits were prepared for subtotal thyroidectomies. The remaining seven cases were again placed on propylthiouracil and regained a euthyroid state. Three patients are still inconsistent in following prescribed therapy.

Some relapses occurred before withdrawal of propylthiouracil. In eight cases, previously well controlled, exacerbations of hyperthyroidism developed when the dosage of propylthiouracil was reduced. Euthyroidism was regained in each instance when dosage was restored to its previous level. Moreover, in four patients who had been well controlled on propylthiouracil and strong

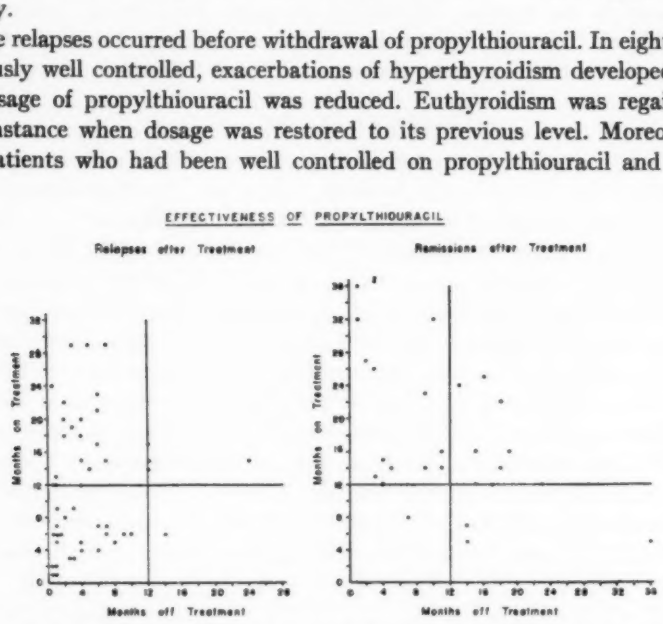


FIG. 4. Only four of 28 patients who received propylthiouracil for less than one year have had a remission exceeding six months. Twenty-four of 48 long term patients have had a recurrence of hyperthyroidism after withdrawal of treatment.

solution of iodine, recurrence of mild hyperthyroidism occurred when iodine was discontinued; in two of these control of the disease was regained when propylthiouracil dosage was increased and in two when iodine was reinstituted.

The drug has been discontinued in 48 long term cases (Table 4). Of these, 24 (50%) relapsed, and 24 (50%) are in remission. The 24 patients with relapsing hyperthyroidism had previously received continuous treatment for an average duration of 18.2 months following which they experienced a temporary remission averaging 5.6 months. The 24 patients now in remission have been followed on the average for 9.7 months, after having previously received continuous propylthiouracil therapy for an average of 20.9 months.

Williams and his coworkers (18) stressed the relationship of glandular size, sex and toxicity to the ultimate outcome of medical therapy. They observed

that permanent remission was more likely to occur in a woman with small goiter and mild thyrotoxicosis. Similarly, in our series (Table 4) patients with small goiter were more likely to experience remission; contrarily, men had a slightly more favorable outcome than women. The initial severity of the thyrotoxicosis was assessed by clinical and laboratory means in the patients with later relapse or remission. In general those patients now in remission manifested milder disease prior to treatment than those who have relapsed after discontinuance of propylthiouracil.

The prediction of the ultimate thyroid status after discontinuance of therapy is difficult, even in patients who in the physician's judgment have received maximum benefit from a prolonged course of therapy. In 32 (64.5%) of the

TABLE 4

Recurrences and Remissions in 48 Patients After Completion of Long Term Propylthiouracil Therapy

	TYPE OF GOITER						SEX				GLANDULAR SIZE†
	Diffuse		Nodular		Recurrent*		Male		Female		
	Number	%	Number	%	Number	%	Number	%	Number	%	
Relapse 24 patients	23	96	0	0	1	4	5	21	19	79	2-3-4-5 × Normal
% relapse	56		0		25		42		53		
Remission 24 patients	18	75	3	12.5	3	12.5	7	29	17	71	1-2-3 × Normal
% remission	44		100		75		58		47		
Total 48 patients	41	86	3	6	4	8	12	25	36	75	

* Recurrent goiter with hyperthyroidism after previous subtotal thyroidectomy.

† At onset of treatment as estimated by palpation.

48 long term cases the drug was discontinued by the physician, and 20 (62.5%) of these 32 maintained a remission. In the remaining 16 cases the drug was discontinued by the patient without the physician's advice, and *only* four (25.0%) experienced a remission.

PROLONGED TREATMENT WITH PROPYLTHIOURACIL

At present the effect of uninterruptedly administered propylthiouracil is being observed in 27 long term patients. Continuous medical management has been maintained for 12 to 48 months with an average duration of 24.7 months; nine patients have been treated each for more than three years. All patients have remained clinically euthyroid showing no deleterious effects to this prolonged therapy. Refractiveness of the disease to propylthiouracil has not been observed. Included in this group are several patients with associated disorders

known to aggravate the control of hyperthyroidism, such as diabetes, asthma, hypertension, cardiac incompetency and emotional instability.

TOXICITY

The toxicity of thiouracil was found to be of such frequency and gravity that its clinical use is no longer sanctioned (52). The toxic reactions to propylthiouracil, however, have been limited to urticaria and dermatitis (25, 26, 53), fever (53, 54), loss of hair (55, 56), leukopenia and granulocytopenia (14, 25, 57), agranulocytosis (58, 59, 60, 61, 62) and thrombopenic purpura (63). In this series of 203 cases, toxicity to propylthiouracil was manifested by mild leukopenia in 26 cases, agranulocytosis in one, eosinophilia in three, urticaria in two and possible lupus erythematosus-like reaction in one.

Leukopenia and granulocytopenia: A leukopenia has occasionally been found in untreated hyperthyroidism. In 5 patients of this series (2.5%) the initial white blood cell count prior to treatment was from 3,150 to 3,950 cells per mm.^{3} with 40 to 68% polymorphonuclear cells.

During treatment 26 (12%) of the 203 cases had white blood cell counts below 4,000 cells per mm.^{3} on one or more occasions. In most instances this leukopenia was noted in the patients treated for prolonged periods, and on the average developed 4.1 months following institution of treatment. In some instances the low white blood cell count was verified by an immediate repeat count, and a differential count was done. In no case was the dosage of propylthiouracil lowered or discontinued because of the leukopenia. As a rule, the white blood cell count was normal within a few days, but in three patients it remained at leukopenic levels for several months without apparent deleterious effects. In these patients the white blood cell counts ranged from 2,000 to 3,900 cells per mm.^{3} with an average of 3,200 cells per mm.^{3}

Granulocytopenia during therapy was considered of more ominous significance than leukopenia. Twelve of the 26 patients with leukopenia also developed a fall in granulocytes to less than 50 per cent of the total white blood cell count. The lowest level encountered was 27 per cent granulocytes. However, in all but one case the granulocytopenia was transient, and normal differential counts were soon noted without change in medication. The following case is the example of persistent leukopenia with associated granulocytopenia:

I. N. (Unit No. 474241), a 34 year old colored housewife with classical Graves' disease of 2 months duration, had a white blood cell count of 5,000 cells per mm.^{3} with 67% polymorphonuclear cells prior to treatment. After two weeks of propylthiouracil 300 mg. daily, the white blood cell count was 4,200 cells per mm.^{3} with 35% polymorphonuclear cells. The hyperthyroidism responded satisfactorily to therapy, but the white blood cell count varied from 2,350 to 5,700 cells per mm.^{3} with 31% to 58% polymorphonuclear cells during 18 months of continuous therapy. On one occasion after 15 months of treatment, when 31% polymorphonuclear cells were found, an aspiration of sternal marrow was performed. The marrow cells and the differential count of marrow cells were normal.

Agranulocytosis: One patient of this series developed agranulocytosis, representing an incidence of 0.5%. A summary is presented:

D. G. (Unit No. 524149), a 44 year old white housewife, was admitted to the Henry Phipps Psychiatric Clinic in an acute depression. She had had two previous depressive episodes. Two of the patient's older sisters had had Graves' disease and were successfully treated by subtotal thyroidectomy. Ten months prior to admission the patient developed heat intolerance, tremor, excessive perspiration, mild diarrhea and palpitation. Her eyes became prominent and the thyroid gland was enlarged. She lost 21 pounds. In June, 1949, her physician found the basal metabolic rate to be plus 70% normal standard, and 300 mg. propylthiouracil daily was begun. Within 6 weeks the basal metabolic rate was plus 13% normal standard, and the dosage of propylthiouracil was reduced to 200 mg. daily. At this time the white blood cell count was said to have been 5,000 cells per mm.^{3} During the next four months the patient was not seen again by her physician, but she continued to take propylthiouracil.

On admission to the hospital on November 17, 1949, she appeared well nourished but mentally depressed. There was slight exophthalmos. The thyroid gland was diffusely enlarged without thrill or bruit. There was no evidence of overt hyperthyroidism. The white blood cell count was 2,250 cells per mm.^{3} On November 18th the white blood cell count was 1,400 cells per mm.^{3}, and the differential count showed 15% polymorphonuclear cells, 78% lymphocytes and 7% monocytes. Since the patient gave no history of taking drugs other than propylthiouracil, except for an occasional aspirin tablet, it seemed probable that she had leukopenia due to propylthiouracil and the drug was immediately discontinued.

On November 18th smears of aspirated sternal marrow showed a cellular marrow with increased numbers of megakaryocytes, a high proportion of metamyelocytes and an almost complete absence of mature granulocytes. This was interpreted as showing maturation arrest of the myeloid series, consistent with acute agranulocytosis. On November 19th a white blood cell count was 1,600 cells per mm.^{3} and the differential count showed 2% myeloblasts, 10% juvenile neutrophiles, 13% segmented neutrophiles, 1% basophiles, 2% young lymphocytes, 70% lymphocytes and 2% monocytes. The patient was given penicillin and folic acid. She was placed on mask isolation. For two weeks the temperature varied between 100° and 101°F.

On November 25th the white blood cell count was 5,000 cells per mm.^{3} with 2% juveniles, 54% polymorphonuclear cells, 1% basophiles, 38% lymphocytes, and 5% monocytes. On November 26th penicillin was discontinued. On December 12th the white blood cell count was 4,600 with a normal differential count save for 2% myeloblasts. On December 15th the basal metabolic rate was plus 5% normal standard. A radioiodine tracer test showed the thyroid to have a "high normal" avidity for radioiodine.

The limited period of propylthiouracil made the likelihood of an enduring remission dubitable, and since the patient was emotionally unstable, it was elected to carry out subtotal thyroidectomy while she remained in a euthyroid status. She was, therefore, placed on strong solution of iodine on December 18th, and operation was performed on December 21st. She has remained well since the operation.

Eosinophilia: Three patients showed a persistent eosinophilia of 6 to 18% during propylthiouracil administration. In two, strong solution of iodine was given concurrently and may account for this finding. In one instance the eosinophilia was associated with leukopenia.

Hypersensitivity reactions: Two patients (1.0%) of this series showed sensi-

tivity to propylthiouracil manifested by generalized urticaria. The urticaria developed on the 14th day of treatment, slowly regressed after its discontinuance, only to reappear within 3 or 4 days when therapy was reinstituted.

Dr. Walter L. Winkenwerder, using a method described by Leftwich (64) for determination of hypersensitivity to the sulfonamides, demonstrated sensitivity to propylthiouracil in these patients by the following procedure: Serum was obtained from an untreated hyperthyroid subject and again during propylthiouracil therapy. In the patients who had formerly had urticaria the intracutaneous injection of pretreatment serum produced only a minute reaction, but injection of serum obtained during treatment produced definite wheal-erythema reactions. The intracutaneous injection of propylthiouracil produced no reaction. In addition, in one patient circulating reagins to propylthiouracil were demonstrated by passive transfer technique: wheal-erythema reactions were obtained at skin sites, sensitized with serum drawn three days after appearance of the urticarial eruption, when tested with serum-propylthiouracil mixtures. In the second patient such tests were negative. It appears, therefore, that these patients are sensitive to an antigen of propylthiouracil linked in some manner to serum protein.

One patient, after receiving continuous propylthiouracil treatment for 27 months, developed low grade fever, pleuritis, pericarditis, hyperglobulinemia and mild pain, erythema and swelling of joints, changes suggesting a collagen vascular disease. The role of propylthiouracil as an etiologic factor cannot be determined, but since this development during therapy appears unique, the case is recorded:

E. S. (Unit No. 463364), a 27 year old colored housewife, was first admitted to the hospital on June 5, 1948, in diabetic coma.

One of the patient's brothers had asthma; another died at 12 years of age of an undiagnosed chronic wasting disease.

In childhood she had several episodes of hoarseness and aphonia; in retrospect these were most likely hysterical. Otherwise, her general health had been good until about 1945, when she noticed the insidious onset of weight loss. For several weeks prior to admission in June, 1948, she had marked polydipsia and polyuria. About three weeks before entry she developed a tremor and shortness of breath on exertion. She began to complain of abdominal pain and two days prior to admission she developed deep respirations with marked weakness, followed by coma. On admission the diagnoses of diabetic acidosis and concomitant exophthalmic Graves' disease were made. She responded satisfactorily to emergency treatment. Thereafter the diabetes was controlled by 32 units of protamine zinc insulin and 20 units of crystalline insulin daily. The thyrotoxicosis was brought under control with propylthiouracil, 300 mg. daily. In the ensuing months the dosage varied between 200 and 300 mg. daily. In November, 1949, the dosage of propylthiouracil was reduced to 150 mg. daily and in January, 1950, to 100 mg. daily; satisfactory control of the hyperthyroidism was maintained. The white blood cell count varied from 3,150 to 5,400 cells per $mm.^3$ with an average count of about 4,100. The polymorphonuclear cells varied from 26 to 55%. Other

than leukopenia and granulocytopenia, no toxic manifestations to propylthiouracil were observed.

In August, 1950, after 27 months of continuous propylthiouracil therapy, she developed migratory swelling and pain of the wrists, ankles and right elbow, shortly followed by feverishness and pleuritic pain over the left lower anterior chest. She was admitted to the hospital on August 31st. Temperature was 100°(F.) rectally, pulse 80 per minute, respirations 20 per minute, and blood pressure 140/90 mm. Hg. She did not appear ill and was in a good state of nutrition. The skin was warm. There was slight exophthalmos. The thyroid was slightly enlarged without thrill or bruit. The heart was not enlarged, the rhythm was regular. A soft systolic murmur was heard at the cardiac apex. The liver and spleen were not palpable. There was discomfort on motion of the left wrist. Over the dorsum of the right foot there was tenderness, increased warmth and slight swelling.

The red blood cell count was 4.6 million cells per mm.^{3}, the hemoglobin 12.8 gm. per 100 cc. and the hematocrit 40%. The sedimentation rate was 46 mm. per hour. The white blood count was 4,100 cells per mm.^{3} with 57% polymorphonuclear cells. Eosinophilia was not noted. The urine was clear, pale and alkaline to litmus paper; it had a specific gravity of 1.022 and contained sugar 4 plus and traces of acetone and protein. On subsequent urinalyses no protein was found.

The mild diabetic acidosis was promptly corrected with additional insulin. During the first five days in the hospital the patient continued mildly febrile, the temperature on one occasion rising to 101°. On the third hospital day a superficial furuncle developed in the region of the left wrist which drained spontaneously; following this the fever subsided slightly. On the fifth hospital day she developed severe pleuritic pain low in the right axilla; a friction rub was heard in this area. A pericardial friction rub was not detected, although the electrocardiogram showed changes consistent with pericarditis; these reverted to normal within one week. Some observers thought that the edge of the liver had become palpable but it was not tender. An x-ray of the chest revealed normal heart and aorta and clear lung fields. Alpha and gamma streptococci were cultured from the nasopharynx. A culture of the uterine cervix was negative for Neisseria. The serum nonprotein nitrogen was 22 mg.%, the serum protein was 7.7 gm.% with an albumin of 3.6 and a globulin of 4.1 gm.%. The serum bilirubin was less than 0.8 mg.%, the cephalin flocculation 2 plus, the thymol turbidity 11 units, the prothrombin time 23 seconds (50% of normal). Basal metabolic rate was plus 3% normal standard. Smears of the peripheral blood for "L.E." cells were negative. Re-examination of the serum proteins confirmed hyperglobulinemia; results of the cephalin flocculation and the thymol turbidity tests remained abnormal.

The diagnosis of a collagen vascular disease such as disseminated lupus erythematosus or acute rheumatic fever was suspected. Propylthiouracil, administration of which was continued during the patient's hospitalization, was withdrawn during the third hospital week because of leukopenia to 2,000 cells per mm.^{3} with 28% polymorphonuclear cells, and, further, because the drug was conceivably the causative agent of the collagen vascular disease-like state. Subsequent to the discontinuance of propylthiouracil the patient's symptoms subsided, and she was discharged from the hospital on September 18, 1950. Two months later hyperglobulinemia was not found; six months later the sedimentation rate was normal.

Ten months after the discontinuance of propylthiouracil the patient had a recurrence of hyperthyroidism. Inasmuch as she had moderately severe diabetes, it was elected not to perform subtotal thyroidectomy, and consequently on September 6, 1951, the patient received 4.5 millicuries of radioiodine (I-131) with complete disappearance of all manifestations of hyperthyroidism. Return of overt clinical and laboratory manifestations of the collagen vascular disease-like state has not occurred.

HYPERCHOLESTEROLEMIA

The rise in serum cholesterol during prolonged therapy was more pronounced in older patients (Figure 3). The mean level of serum cholesterol was 182 mg.% (S.D. = ±48 mg.%) in 21 patients under 40 years of age prior to treatment and 183 mg.% (S.D. = ±43 mg.%) in 27 patients over 40 years of age. The mean increase after one year of treatment was 65 mg.% (S.D. = ±74 mg.%) in the group of younger patients and 95 mg.% (S.D. = ±52 mg.%) in the older patients. Propylthiouracil dosage was similar in both groups. Since the level of serum cholesterol has been shown to rise with increasing age in normal human beings (65, 66, 67), it is probable that the older patients had a greater fall in serum cholesterol than the younger patients upon the development of hyperthyroidism and that the greater rise in the older patients during treatment represents a return to the expected level for this age group. That a rise of serum cholesterol of greater magnitude occurs in the older hyperthyroid patients during antithyroid therapy than in the younger is also noted in the data published by Bartels (28).

However, as noted in Figure 3, the level of serum cholesterol in fourteen patients at one year of continuous therapy was between 300 and 375 mg.%, values considered to be slightly in excess of normal in our laboratory. In these fourteen patients there was no clinical evidence of hypothyroidism and basal metabolic rates were not below the accepted normal range. Dosages of propylthiouracil were comparable to those received by other patients. A reduction of dosage in eight of the fourteen patients was followed by a moderate decrease in the content of the serum cholesterol without relinquishing control of the disease. Since the level of serum cholesterol tends to increase with diminished thyroid activity (67), it is possible that these eight patients were slightly overly treated at the time mild hypercholesterolemia was detected. Thus, a rise in serum cholesterol to an abnormally high value may be a means for detecting early hypofunction of the thyroid gland before other manifestations of hypothyroidism become apparent.

PARATHYROID GLANDS

Recently it has been reported (68) that albino rats fed propylthiouracil over a prolonged period develop hypertrophy and hyperplasia of the parathyroid glands and changes in bone consistent with *osteitis fibrosa cystica generalisata*. In view of this finding, levels of the serum calcium, phosphorus, alkaline phosphatase and protein have been determined in 28 patients who have received prophylthiouracil continually for more than one year, the average being two and a half years. The results of these determinations, recorded in Table 5, have ranged within normal limits except as noted in the legend. These data, although not extensive, suggest that should parathyroid hyperplasia occur

during prolonged propylthiouracil therapy, it is not reflected by alterations in serum calcium, phosphorus or alkaline phosphatase. Further evidence that parathyroid hyperplasia with prolonged propylthiouracil therapy is unlikely is shown by the following case:

D. B. (Unit No. 413004), a sixty-one year old colored housewife, was first admitted to the Johns Hopkins Hospital on February 12, 1947, complaining of nervousness, weight loss and weakness since August, 1946. She developed tremor of the hands, intolerance to heat and falling out of the hair. On examination the pulse rate was 86 per minute and the blood pressure 154/74 mm. Hg. Weight loss was apparent. The skin was moist and warm. There was stare and lid lag. The thyroid was diffusely enlarged to about five to six times normal size. A thrill and bruit were present over the gland. The heart was slightly enlarged and a moderately loud systolic murmur was heard over the base of the heart and along the left sternal border. Slight pitting edema of the ankles was present. Urinalysis was normal. The hemoglobin was 10.5 gm. per 100 cc. Basal metabolic rates varied from plus 28 to plus 38%

TABLE 5

Determinations of Serum Calcium, Phosphorous, Alkaline Phosphatase and Protein in Twenty-eight Patients Receiving Propylthiouracil for an Average of Two and One-half Years

	CALCIUM	PHOSPHOROUS	ALKALINE PHOSPHATASE	PROTEIN*
	mg/100 cc	*mg/100 cc*	*Bodansky Units mg/100 cc*	*gm/100 cc*
Average	10.77	3.5	4.49	7.17
Range	9.9–12.3	2.6–4.5	2.0–9.1	5.9–8.5

* Determined by refractive index.

The determinations of serum calcium, phosphorous, alkaline phosphatase and protein are within the limits of normal in our laboratory except as follows: Serum calcium level was 12.3 mg.% in one patient (see D. B. Unit No. 413004 in text), in another patient a single phosphorous determination was 2.6 mg.% with no other abnormality detected, and a third patient with coexistent liver disease had an alkaline phosphatase of 9.1 units.

of normal standard. Determinations of serum cholesterol varied from 188 to 235 mg.%. The diagnosis of diffuse goiter with hyperthyroidism was established, and propylthiouracil, 300 mg. daily, was started on February 25th, and she was discharged from the hospital on March 1st. She improved rapidly with marked weight gain, decrease of basal metabolic rate to normal and rise in serum cholesterol concentration. After eighteen and one-half months of continuous therapy, propylthiouracil was discontinued.

Six months after withdrawal of medication the patient experienced a return of symptoms of hyperthyroidism, and therapy was reinstituted in April, 1949. Response was again satisfactory, and maintenance dosage of 150 mg. of propylthiouracil daily was established. The thyroid gland did not alter in size. In June, 1951, mild diabetes mellitus was detected. A permanent remission of hyperthyroidism seemed unlikely in view of the previous recurrence after withdrawal of treatment and the persistence of the large goiter. Accordingly, after 26 months of therapy in this second course, it was elected to carry out subtotal thyroidectomy.

In June and July, 1951, determinations of serum calcium were respectively 11.9 and 12.8 mg.%, of serum phosphorus 3.3 and 2.1 mg.% and of alkaline phosphatase 7.1 and 6.1 Bodansky units per 100 cc.

On admission to the hospital on July 12, 1951, the patient appeared euthyroid. The diabetes mellitus was controlled by diet and 25 units of NPH insulin daily. At operation on July 21st, a parathyroid gland was inadvertently removed. The histology of this parathyroid gland was normal. Nine days following the operation the serum calcium and phosphorus were 8.7 and 4.3 mg.%, respectively, and 11 days postoperatively 9.5 and 4.0 mg.%, respectively. The patient did not have manifestations of tetany. One month following operation the serum calcium and phosphorus were 10.2 and 2.2 mg.%, respectively.

The patient's convalescence was satisfactory and her diabetes has remained unchanged.

Autopsies were obtained in three patients who died of disease other than hyperthyroidism while they were receiving propylthiouracil. In one patient with recurrent Graves' disease, who five years before had had subtotal thyroidectomy followed by hypocalcemia requiring calcium therapy, the parathyroids were not found. In the remaining two instances the parathyroid glands showed hypertrophy and hyperplasia; one had intercapillary glomerulosclerosis, the other pyelonephritis. Prior to death both had severe renal insufficiency, a disorder frequently leading to parathyroid hyperplasia (69).

ASSOCIATED DISORDERS

Certain disorders, commonly allied with hyperthyroidism, such as diabetes mellitus, may complicate therapeutic management; occasionally serious disorders unrelated to hyperthyroidism occur. In such instances amelioration of hyperthyroidism is of paramount importance. Propylthiouracil is of advantage in the attainment and maintenance of a euthyroid state during the treatment of a serious complicating disorder.

In this series the major complications appearing in conjunction with hyperthyroidism are shown in Table 6. In all instances propylthiouracil effectively controlled the hyperthyroidism, permitting unrestricted treatment of the complication.

Thyrotoxic myopathy: Thyrotoxicosis occasionally presents itself in a masked form manifested most prominently by pronounced muscular wasting and weakness (70). In this series there are ten such cases of thyrotoxic myopathy, seven occurring in men beyond middle age. Some of these patients were studied by Zierler (71), who found an altered creatine metabolism with hypocreatininuria, impaired creatine tolerance and minimal creatinuria. Following institution of propylthiouracil, all patients improved dramatically. Muscle mass returned and strength improved. On the average 90% of the weight lost during the present illness was regained within the first six months of treatment. Two of these patients are in remission after withdrawal of treatment. One patient has had a subtotal thyroidectomy, and seven patients continue to receive propylthiouracil.

Apathetic hyperthyroidism: Seven patients had typical "apathetic thyroidism" (72) with anorexia, weight loss, weakness and apathy. Propylthiouracil therapy of this variant of the disease was equally gratifying, all patients show-

ing marked weight gain, return of strength and well being. Irregularities of cardiac rhythm, frequently encountered prior to treatment in these patients, regressed as control of the disease was obtained.

Cardiac disorders: Twenty-six patients had associated cardiac disturbances. There were 19 women and 7 men whose ages varied from 30 to 72 years of age. Twenty were over the age of 45. Eleven (40.7%) of the 27 patients with nodular goiter showed evidence of associated heart disorder, whereas only 14 (8.8%) of the 158 patients with diffuse goiters were similarly affected. One

TABLE 6

Associated and Complicating Conditions

	NUMBER OF PATIENTS
Heart disease	26
Congestive failure	13
Arrhythmia	8
Congestive failure with arrhythmia	2
Hypertension	3
Diabetes mellitus	14
Pregnancy	15
Gynecological Disorder	5
Hysterectomy for fibroids	4
Cancer of cervix	1
Arthritis	4
Tuberculosis	2
Pulmonary	1
Cervical	1
Cancer of thyroid	2
Therapeutic abortion	2

Each of the following conditions was found once: pernicious anemia, bronchial asthma, lobar pneumonia, bronchiectasis, cerebral thrombosis, eczema, sarcoid, ulcerative colitis, glaucoma, epilepsy, cholecystectomy for stones, and repair of inguinal hernia. Several patients, not included in the table, have had or are receiving treatment for syphilis.

patient of the 16 with recurrent hyperthyroidism after previous thyroidectomy had congestive heart failure. Thus, these data substantiate the observations of Thomas (73) and Andrus (74) who noted the increased frequency of cardiac complications in elderly thyrotoxic patients with nodular goiters.

Fifteen thyrotoxic patients developed congestive heart failure with associated hypertension or arteriosclerotic heart disease. Two of these patients also had auricular fibrillation during failure. In three patients severe hypertension without failure complicated the hyperthyroidism.

Cardiac arrhythmias were present in ten patients, nine had auricular fibrillation and one paroxysmal auricular tachycardia. In all cases a reversion to normal sinus rhythm occurred when adequate treatment was instituted. However, auricular fibrillation recurred following subtotal thyroidectomy in one patient and following reduction in the dosage of propylthiouracil in another

patient. In the latter instance the arrhythmia was corrected by increasing the dosage to its previous level.

Of the 26 patients with associated cardiac disorders, 20 are being maintained in a euthyroid status with propylthiouracil. Successful subtotal thyroidectomy was performed on the remaining patients after preparation with propylthiouracil. One patient, however, had a postoperative recurrence of hyperthyroidism and is now again controlled with propylthiouracil.

Diabetes: Studies of alterations in carbohydrate metabolism during propylthiouracil treatment were made only in patients with frank diabetes mellitus, and thus no data have been accumulated regarding the effect of propylthiouracil on the masked diabetic-like tendency frequently observed in thyrotoxic patients. The association of diabetes mellitus with hyperthyroidism was present in 14 (6.9%) patients of this series, a greater frequency than previously reported (75). There were ten women and four men with ages ranging from 25 to 72 years. Nine patients were over the age of 40 years. In 12 cases the diabetes had been present for one to 20 years prior to the onset of the hyperthyroidism, and in most instances it was mild, being controlled by diet alone or by small dosages of insulin. In two instances hyperthyroidism had been present for several years prior to the development of diabetes. One of the two patients developing diabetes during propylthiouracil therapy was approximately 15 pounds overweight prior to treatment. During therapy she gained 35 pounds. Her diabetes may well have been related to the development of this obesity. In most diabetic patients requiring insulin prior to the treatment of hyperthyroidism, the insulin dosage necessary for control of the diabetes was reduced or discontinued as propylthiouracil-induced euthyroidism was attained. In two patients propylthiouracil was discontinued after prolonged therapy. During the subsequent remissions which have persisted for approximately one year, the diabetes of each patient has not appreciably changed.

Three diabetic thyrotoxic patients have died. For long periods prior to death each patient had been euthyroid on propylthiouracil therapy. One patient died in hypertensive cardiac failure. Two patients died in uremia and were found at autopsy to have the renal lesions of intercapillary glomerulosclerosis as described by Kimmelstiel and Wilson (76).

SUMMARY

Propylthiouracil effectively ameliorates thyrotoxicosis, and, as a relatively non-toxic agent, is now well established in the therapeutic armamentarium of this disease. Successful treatment necessitates adequate dosage and cooperation on the part of the patient. Since proper treatment returns the metabolic status to normalcy, the drug not only is an important adjuvant in the preoperative medication for subtotal thyroidectomy, but also can be administered for prolonged periods in anticipation of obtaining eventual remission of the

disease. Moreover, propylthiouracil is inexpensive and readily available, and most patients can be treated without hospitalization.

Two hundred and three hyperthyroid patients have been treated with propylthiouracil. The minimal initial dosage exhibiting optimal effectiveness was found to be 300 mg. daily.

Of the 203 patients, 21.7% were prepared for subtotal thyroidectomy, 16.8% failed to return after a few visits, 5.4% were transferred to the care of their personal physicians, and 56.1% have been carried on prolonged therapy.

Rate of response to therapy was variable, but on the average the basal metabolic rate was within normal range within approximately 90 to 100 days. In patients with marked weight loss prior to treatment, there was a rapid gain in weight during treatment, although six to twelve months was required before weight was normal. The serum cholesterol concentration rose abruptly during the first two months of therapy, with only slight increase noted with further treatment.

During prolonged therapy increase in goiter size occurred in only four instances, whereas diminution in goiter size was frequently observed. Indeed, the gland became impalpable in one-third of the patients with diffuse goiter; this decrease in size usually occurred after many months of treatment.

A significant increase of exophthalmos occurred in five of 52 patients with diffuse goiter during prolonged treatment; malignant exophthalmos was not observed. The data suggest that propylthiouracil may be the most prudent form of treatment of exophthalmic Graves' disease.

A long lasting remission has been obtained in 24 of 48 patients following removal of the drug after protracted therapy. In the 24 patients who had a recurrence of hyperthyroidism, the relapse usually appeared within six months subsequent to withdrawal of therapy.

Toxic reactions to propylthiouracil were leukopenia with granulopenia (12 cases), agranulocytosis (1 case), urticaria (2 cases), and a collagen vascular disease-like state (1 case).

Major surgical operations have been successfully accomplished and serious illnesses satisfactorily treated in patients receiving maintenance dosage of propylthiouracil. In those patients in whom subtotal thyroidectomy is contraindicated, continuous administration of the drug has brought gratifying results. While the ablative forms of treatment of thyrotoxicosis are usually successful in eradicating this disease, constant control is possible through prolonged, continuous administration of propylthiouracil.

ACKNOWLEDGEMENTS

The authors express their appreciation to the physicians of the Thyroid Clinic cooperating with us in this study. The attention given their patients, as well as their care in the recording of details, made the study possible. We appreciate the devoted service of our

Social Service workers, Miss Regina Slaughter and Mrs. Virginia Lane Magladery, and our clinic nurses, Mrs. Sarah Green and Miss Eleanor Rulis. The kind assistance of the clinic secretaries, Miss Marilyn Goldstein, Miss Claire Schaake and Mrs. Jacqueline Linderman, is gratefully acknowledged. To the many technicians under the direction of Miss Regina Weistock, Mrs. Florence White and Miss Ruth Murphy we express appreciation for the numerous laboratory tests willingly and carefully accomplished. We are indebted to Dr. Walter L. Winkenwerder for his study of the patients with urticaria and to Dr. C. Lockard Conley, who examined the bone marrow smears. To Dr. John Eager Howard we are grateful for clinical counsel throughout the study.

REFERENCES

1. a. Chesney, A. M., Clawson, T. A. and Webster, B.: Endemic goiter in rabbits; I. Incidence and characteristics. Bull. Johns Hopkins Hosp. **43:** 261 (1928).
   b. Webster, B., Clawson, T. A. and Chesney, A. M.: Endemic goiter in rabbits; II. Heat production in goitrous and non-goitrous animals. Bull. Johns Hopkins Hosp. **43:** 278 (1928).
   c. Webster, B. and Chesney, A. M.: Endemic goiter in rabbits; III. Effect of administration of iodine. Bull. Johns Hopkins Hosp. **43:** 291 (1928).
2. MacKenzie, J. B., MacKenzie, C. G. and McCollum, E. V.: Effect of sulfanilylguanidine on thyroid of rat. Science **94:** 518 (1941).
3. MacKenzie, C. G. and MacKenzie, J. B.: Effect of sulfonamides and thioureas on the thyroid gland and basal metabolism. Endocrinology **32:** 185 (1943).
4. Richter, C. P. and Clisby, K. H.: Toxic effects of the bitter-tasting phenylthiocarbamide. Arch. Path. **33:** 46 (1942).
5. Kennedy, T. H.: Thioureas as goitrogenic substances. Nature, London, **150:** 233 (1942).
6. Astwood, E. B.: Treatment of hyperthyroidism with thiourea and thiouracil. J. Am. Med. Assn. **122:** 78 (1943).
7. Williams, R. H.: Antithyroid drugs, with particular reference to thiouracil. Arch. Int. Med. **74:** 479 (1944).
8. Himsworth, H. P. and Joll, C. A.: Discussion of thiouracil and thiourea in treatment of thyrotoxicosis. Proc. Roy. Soc. Med. **37:** 693 (1944).
9. Astwood, E. B.: Thiouracil treatment in hyperthyroidism. J. Clin. Endocrinol. **4:** 229 (1944).
10. Newman, E. V.: Thiouracil and hyperthyroidism. M. Clin. North America **29:** 302 (1945).
11. Moore, F. D.: Toxic manifestations of thiouracil therapy. J. Am. Med. Assn. **130:** 315 (1946).
12. McGinty, D. A. and Bywater, W. G.: Antithyroid studies; goitrogenic activity of some thioureas, pyrimidines and miscellaneous compounds. J. Pharmacol. & Exper. Therap. **84:** 342 (1945).
13. Astwood, E. B., Bissell, A. and Hughes, A. M.: Antithyroid activity of thiobarbital (5,5-diethyl-2-thiobarbituric acid). Endocrinology **36:** 72 (1945).
14. Lahey, F. H. and Bartels, E. C.: Use of thiouracil, thiobarbital and propylthiouracil in patients with hyperthyroidism. Ann. Surg. **125:** 572 (1947).
15. Bartels, E. C.: Propylthiouracil; its use in preoperative treatment of severe and complicated hyperthyroidism. West. J. Surg. **56:** 226 (1948).
16. Crile, G., Jr.: Indications for thyroidectomy for hyperthyroidism. West. J. Surg. **55:** 573 (1947).

17. Astwood, E. B.: Treatment of hyperthyroidism with antithyroid compounds. *Advances in Internal Medicine.* New York. Interscience Publishers. **3:** 237 (1949).
18. Williams, R. H., Asper, S. P., Jr., Rogers, W. F., Jr., Myers, J. D. and Lloyd, C. W.: Persistence of remissions of thyrotoxicosis after cessation of thiouracil therapy. New England J. Med. **236:** 737 (1947).
19. Lahey, F. H.: Thiouracil, thiobarbital, propylthiouracil and treatment of hyperthyroidism. Postgrad. Med. **1:** 126 (1947).
20. Starr, P., Petit, D. W., Meister, L. and Stirrett, R. L.: Therapeutic studies in hyperthyroidism; propylthiouracil. J. Clin. Endocrinol. **9:** 330 (1949).
21. Williams, R. H.: Selection of therapy for individual patients with thyrotoxicosis. J. Am. Med. Assn. **139:** 1064 (1949).
22. Beierwaltes, W. H. and Sturgis, C. C.: Current methods of treating thyrotoxicosis. M. Clin. North America **33:** 497 (1949).
23. Christensen, H. N. and Cooper, P. F.: Quoted by Astwood, E. B.; see ref. 17.
24. Rogers, W. F., Jr., Asper, S. P., Jr. and Williams, R. H.: Clinical significance of malignant neoplasm of the thyroid gland. New England J. Med. **237:** 569 (1947).
25. McCullagh, E. P., Hibbs, R. E. and Schneider, R. W.: Propylthiouracil in the treatment of hyperthyroidism. Am. J. M. Sc. **214:** 545 (1947).
26. Astwood, E. B. and Vanderlaan, W. P.: Treatment of hyperthyroidism with propylthiouracil. Ann. Int. Med. **25:** 813 (1946).
27. Peters, J. P. and Man, E. B.: The significance of serum cholesterol in thyroid disease. J. Clin. Investigation **29:** 1 (1950).
28. Bartels, E. C.: Basal metabolic rate and plasma cholesterol as aids in the clinical study of thyroid disease. J. Clin. Endocrinol. **10:** 1126 (1950).
29. Poppen, J. L.: The surgical treatment of progressive exophthalmos. J. Clin. Endocrinol. **10:** 1231 (1950).
30. Hertz, S., Means, J. H. and Williams, R. H.: Graves' disease with dissociation of thyrotoxicosis and ophthalmopathy. West. J. Surg. **49:** 493 (1941).
31. Soley, M. H.: Thiouracil in thyroid diseases. California Med. **66:** 75 (1947).
32. Woods, A. C.: Ocular changes of primary diffuse toxic goiter. Medicine **25:** 113 (1946).
33. Dobyns, B. M. and Haines, S. F.: Changes in prominence of eyes in various thyroid states. J. Clin. Endocrinol. **6:** 633 (1946).
34. Cattell, R. B.: Eye complications in exophthalmic goiter; cataracts and exophthalmos. Ann. Surg. **100:** 284 (1934).
35. Barr, D. P.: Critical evaluation of thiouracil and the newer related compounds in treatment of thyroid disease. Bull. New York Acad. Med. **24:** 287 (1948).
36. Danowski, T. S., Man, E. B., Elkington, J. R., Peters, J. P., and Winkler, A. W.: Results of prolonged medical treatment of hyperthyroidism with thiourea. Am. J. Med. Sc. **215:** 123 (1948).
37. Watson, E. M.: Thiouracil in control of thyrotoxicosis. J. Clin. Endocrinol. **5:** 273 (1945).
38. Rose, E. and McConnell, J.: Thiouracil in thyrotoxicosis; results of prolonged treatment in 35 cases. Am. J. Med. Sc. **213:** 74 (1947).
39. Greenberg, S. U. and Bruger, M.: Observations on the prolonged medical management of toxic diffuse goiter with thiouracil and propylthiouracil. Am. J. Med. Sc. **220:** 373 (1950).
40. Astwood, E. B.: Clinical use of the antithyroid drugs. *Progress in Clinical Endocrinology.* Soskin, S., editor. Grune & Stratton, New York (1950).
41. Taylor, N., Large, A. and Noth, P.: Propylthiouracil in thyrotoxicosis; alternate cases treated medically and surgically. Am. J. Med. Sc. **220:** 362 (1950).

42. MEANS, J. H.: Hyperophthalmopathic Graves' disease. Ann. Int. Med. **23:** 779 (1945).
43. THOMAS, H. M., JR.: Exophthalmos in the light of current anti-thyroid therapy. Am. J. Med. **11:** 581 (1951).
44. HOWARD, J. E.: Personal communication.
45. MADDOX, K.: Control of hyperthyroidism by propylthiouracil; clinical inquiry. M. J. Australia **2:** 113 (1949).
46. PEMBERTON, J. DE J., HAINES, S. F. AND KEATING, F. R., JR.: Current treatment of hyperthyroidism. J. Clin. Endocrinol. **9:** 1232 (1949).
47. KENT, G. T., SHIPLEY, R. A. AND RUNDELL, K. D.: Thiourea compared with propylthiouracil in treatment of thyrotoxicosis. Am. J. Med. Sc. **217:** 627 (1949).
48. SEED, L. AND LINDSAY, A. M.: Hyperthyroidism in the aged; a review of 100 cases over 60 years of age. Geriatrics **4:** 136 (1949).
49. COLE, W. H.: Treatment of hyperthyroidism. Mississippi Doctor **25:** 93 (1947).
50. ROWE, P. G.: Propylthiouracil in the treatment of hyperthyroidism. Canad. Med. Assn. J. **60:** 460 (1949).
51. BEIERWALTES, W. H. AND STURGIS, C. C.: The present status of the treatment of thyrotoxicosis. Practitioner, London **162:** 486 (1949).
52. Council on pharmacy and chemistry. J. Am. Med. Assn. **136:** 691 (1948).
53. MCGAVACK, T. H., GERL, A. J., VOGEL, M. AND SCHUTZER, S.: Clinical comparison of effectiveness of 6-*n*-propylthiouracil and 2-thiouracil as antithyrotoxic agents. Am. J. Med. **2:** 144 (1947).
54. REVENO, W. S.: Propylthiouracil in thyrotoxicosis; observations on 54 patients. J. Am. Med. Assn. **133:** 1190 (1947).
55. Loss of hair following use of propylthiouracil. Queries and minor notes. J. Am. Med. Assn. **143:** 860 (1950).
56. WILBURNE, M.: Hair loss and pigmentation due to thiouracil derivatives. J. Am. Med. Assn. **147:** 379 (1951).
57. EISENMENGER, W. J. AND STEELE, J. M.: Leukopenia following the use of propylthiouracil. J. Am. Med. Assn. **135:** 510 (1947).
58. LIVINGSTON, H. J. AND LIVINGSTON, S. F.: Agranulocytosis and hepatocellular jaundice; toxic reaction following propylthiouracil therapy. J. Am. Med. Assn. **135:** 422 (1947).
59. BARTELS, E. C.: Agranulocytosis during propylthiouracil therapy. Am. J. Med. **5:** 48 (1948).
60. PARKS, A. E.: Hyperthyroidism treated with propylthiouracil. Canad. Med. Assn. J. **59:** 64 (1948).
61. FUTCHER, P. H. AND MASSIE, E.: Agranulocytosis due to propylthiouracil. Ann. Int. Med. **32:** 137 (1950).
62. JULIAR, B. AND HARRIS, T. L.: Fatal agranulocytosis occurring during propylthiouracil therapy. J. Am. Med. Assn. **139:** 646 (1949).
63. FEWELL, R. A., ENGEL, E. F. AND ZIMMERMAN, S. L.: Acute thrombopenic purpura associated with administration of propylthiouracil. J. Am. Med. Assn. **143:** 891 (1950)
64. LEFTWICH, W. B.: An intradermal test for the recognition of hypersensitivity to the sulfonamide drugs. Bull. Johns Hopkins Hosp. **74:** 26 (1944).
65. HURXTHAL, L. M. AND SIMPSON, H. N.: Hypothyroidism; hypercholesterolemia. J. Clin. Endocrinol. **1:** 450 (1941).
66. SPERRY, W. M. AND WEBB, M.: The effect of increasing age on serum cholesterol concentration. J. Biol. Chem. **187:** 107 (1950).
67. PETERS, J. P. AND MAN, E. B.: Interrelations of serum lipids in normal persons. J. Clin. Investigation **22:** 707 (1943).

68. MALCOLM, J., GRIESBACH, W. E., BIELSCHOWSKY, F. AND HALL, W. H.: Hyperplasia of the parathyroids associated with osteitis fibrosa in rats treated with thiouracil and related compounds. Brit. J. Exper. Path. **30:** 17 (1949).
69. PAPPENHEIMER, A. M. AND WILENS, S. L.: Enlargement of the parathyroid glands in renal disease. Am. J. Path. **11:** 73 (1935).
70. MCEACHERN, D. AND ROSS, W. D.: Chronic thyrotoxic myopathy; a report of three cases with a review of previously reported cases. Brain **65:** 181 (1942).
71. ZIERLER, K. L.: Muscular wasting of obscure origin and the thyroid gland. Bull. Johns Hopkins Hosp. **89:** 263 (1951).
72. LAHEY, F. H.: Apathetic thyroidism. Ann. Surg. **93:** 1026 (1931).
73. THOMAS, H. M., JR.: Nodular goiter with hyperthyroidism. Arch. Surg. **16:** 117 (1928).
74. ANDRUS, E. C.: Heart in hyperthyroidism; clinical and experimental study. Am. Heart J. **8:** 66 (1932).
75. ANDRUS, E. C.: Hyperthyroidism and diabetes mellitus. Bull. Johns Hopkins Hosp. **50:** 383 (1932).
76. KIMMELSTIEL, P. AND WILSON, C.: Intercapillary lesions in glomeruli of kidney. Am. J. Path. **12:** 83 (1936).

STUDIES ON A CHEMICAL CONTINUUM*

W. MANSFIELD CLARK

Department of Physiological Chemistry, The Johns Hopkins University School of Medicine

Received for publication February 11, 1952

For the purposes of his systematic science the chemist regards as distinct any process that, by control of conditions, he can study as an isolated process. However, he can cite many cases in which two or more processes are combined. It is my present purpose to show by a series of concrete cases how three different processes are integrated in what, for lack of a better term, may be called by the somewhat highfalutin term a *chemical continuum*.

I shall illustrate by going stepwise from brief mention of proton exchange to oxidation-reduction equilibria and thence to those studies of metalloporphyrins that my graduate students, fellows and I have been carrying on for several years.

The details would, I am sure, bore most of you beyond endurance. Therefore, I shall give only enough to suggest the validity of assertions with which I sketch the developments. The time being properly limited, you will, I hope, pardon me for omitting references to the voluminous literature and for using as illustrative data only those obtained in our laboratory.

One likes to know what led to a particular research.

Thrilling events in the history of biochemistry were identifications of several substances, which students of nutrition were calling by the nondescript term, vitamins, as precursors of parts of specific enzymes. One example is the antipellagra factor which is built into coenzymes I and II, the phosphopyridine nucleotides. Another is vitamin B_2 which is built into flavin adenine dinucleotide. In each of these cases there is needed the cooperation of one or another specific protein to form a complete enzyme system. Ordinarily regarded to be

* This article, after some revision, is substantially that read at the meeting of the Johns Hopkins Medical Society on December 10, 1951.

The proper limitation of time (and now of space) and the fact that this is a presentation of concepts, rather than a documentation of the data on which the concepts are based, made it advisable to omit references to the literature. Because the author is indebted to so many pioneers in the fields briefly reviewed as well as to his associates and students, he feels that he should give at least a central reference. Original articles on metalloporphyrins up to 1949 are cited and discussed in the comprehensive treatise *Hematin Compounds and Bile Pigments* by Lemberg and Legge. Particular mention should be made of the pioneer studies of the potentials of systems containing heme by J. B. Conant and his students and by E. S. G. Barron and his associates. The recent work of Robert Cowgill will be published soon.

The elementary theories of acid-base equilibria and oxidation-reduction equilibria with citation of a few original papers will be found in the author's *Topics in Physical Chemistry*, 2nd edition, 1952.

in another category are enzymes such as hemoglobin, cytochrome *c*, etc., each of which contains the iron porphyrin commonly called heme. In hemoglobin, for example, heme is regarded as a prosthetic compound,—prosthetic because it adds to a protein to complete it for a particular function. For convenience we may extend the term prosthetic compound to the substances first mentioned, to flavin adenine dinucleotide, for example.

In each of the prosthetic compounds mentioned there is a unique structure that may be modified by loss, or gain, of electrons. You hardly need to be reminded that for historical reasons the chemist speaks of loss of electrons as oxidation and gain of electrons as reduction. The conversion of the ferrous ion to the ferric ion by transfer of an electron to an electron acceptor, or the conversion of hemoglobin to methemoglobin by transfer of four electrons from the "irons" to an electron acceptor, is called *oxidation*. In distinction therefrom the addition of oxygen to hemoglobin to form oxyhemoglobin without change of the state of the "iron" may be called *oxygenation*. A mixture of the oxidized and reduced forms of one of the prosthetic compounds constitutes an oxidation-reduction system. For present purposes we may say that a given oxidation-reduction system in a given state has an electron escaping tendency.

These prosthetic compounds are also subject to ionization as acids or bases, to exchanges of protons.

Interest may center upon the acid-base equilibria in exchange of protons. Or interest may center upon the oxidation-reduction equilibria in transfer of electrons. Having developed some of the principles and techniques of these two subjects we felt we had a sound basis from which to start exploration of another set of relations.

In figure 1 prosthetic compounds are at the left. They are represented as in the oxidized and in the reduced states. In each case the prosthetic compound can combine with one or another suitable substance which we call, in general, a ligand (that which is tied). Among the enzymes there are different degrees in the strength of the bonding between prosthetic compound and specific protein. In hemoglobin and its oxidation product, methemoglobin, the bonding is strong. In some other cases it is relatively weak. But whether the bonding is strong or weak there arises this first question: What modification of the electron escaping tendency, exhibited by the prosthetic system, follows the incorporation of oxidant and reductant in complexes? Second; suppose the complexes form reversibly so that in the same solution there will be uncombined prosthetic compound in both oxidized and reduced states, uncombined ligand and both oxidized and reduced complexes. Suppose also that each component can serve as a proton donor or as a proton acceptor in one or another region of pH. How shall we formulate the equilibrium states of so complex a system in such a way as to make them subject to experimental evaluation?

I have mentioned the fact that a specific protein must cooperate with one

of the prosthetic compounds to complete an enzyme system. Now proteins are delicate compounds easily altered by rough handling and subject to various chemical changes. So it seemed advisable to start the development of principles with simpler compounds. Having chosen a metalloporphyrin as a prosthetic compound subject to oxidation and reduction, we used pyridine, cyanide, imidazole, etc., as simple compounds known to combine reversibly with metalloporphyrins.

No effort was made to use these systems as catalysts. No effort was made to find practical applications. The only matter in mind, and one that required full attention, was the elucidation of certain general principles for which these systems seem to be well adapted.

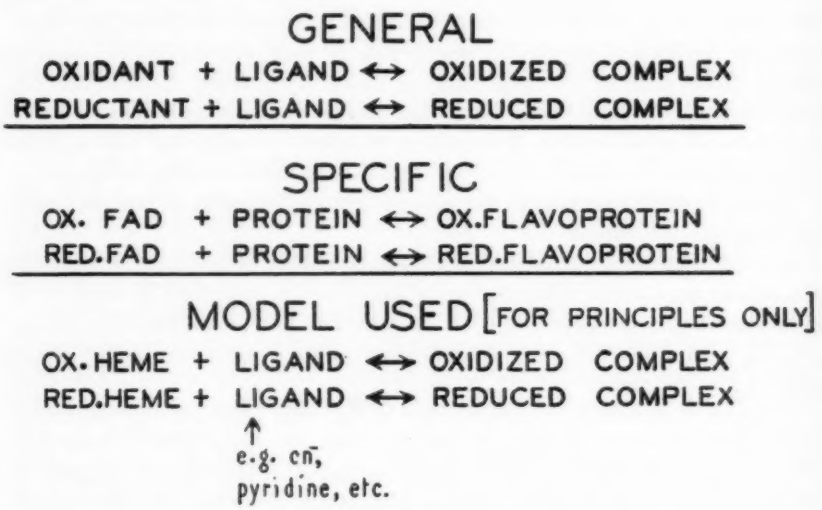

GENERAL
OXIDANT + LIGAND ↔ OXIDIZED COMPLEX
REDUCTANT + LIGAND ↔ REDUCED COMPLEX
SPECIFIC
OX. FAD + PROTEIN ↔ OX.FLAVOPROTEIN
RED.FAD + PROTEIN ↔ RED.FLAVOPROTEIN
MODEL USED [FOR PRINCIPLES ONLY]
OX. HEME + LIGAND ↔ OXIDIZED COMPLEX
RED.HEME + LIGAND ↔ REDUCED COMPLEX
e.g. CN⁻,
pyridine, etc.

FIG. 1

It should not be inferred that the problems stated here in broad terms had not been seen and attacked by others. The lines of attack we have followed involve the well delineated theory of acid-base equilibria with its common measure called pH and the well delineated, restricted theory of oxidation-reduction equilibria applicable when there is the common measure electrode potential. These are used in such a manner as to reveal both their interrelation and particularly to show the relation of one system to another. Did time permit, it would be possible to show that these and another parameter to be mentioned can be incorporated in data on changes of free energy, thus tying together in terms of energy changes what otherwise would be considered isolated examples of material changes.

It is essential to my theme to present in broad outline one or two of the complexities encountered and perhaps it is well to sketch briefly one of the experimental methods.

Figure 2 represents a simple, special, electric cell. As you know, when chlorine is added directly to an iodide the iodide reduces the chlorine to chloride, the chlorine oxidizes the iodide to iodine. In this cell chlorine and iodide are held apart by a bridge of agar containing KCl. Nothing happens except a slow

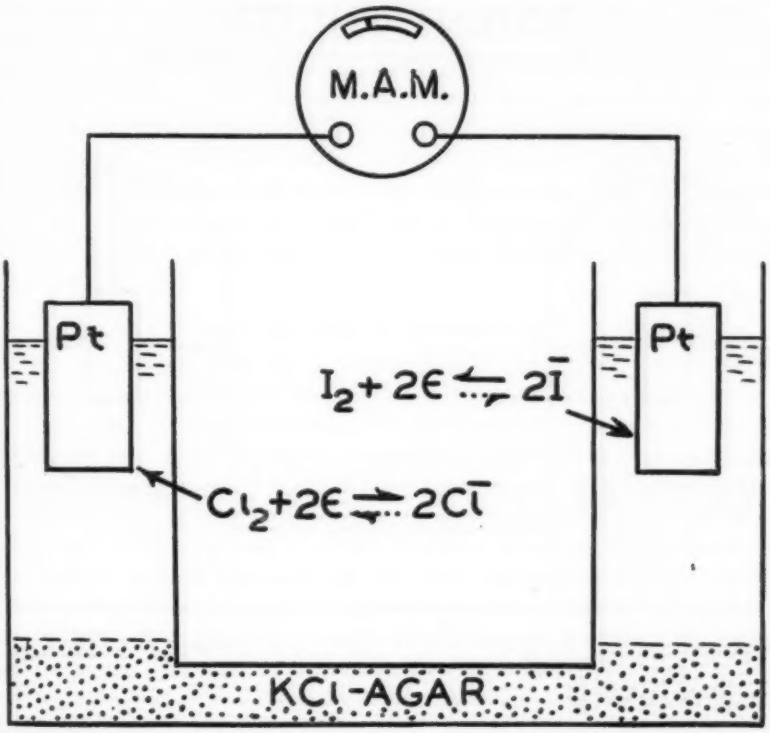


FIG. 2. A simple electric cell. Diagrammatic. ϵ = electron. M.A.M. = milliammeter.

diffusion into the agar until the metal electrodes are put into metallic contact. Because the escaping tendency of the electrons in the iodide-iodine system is greater than that of the chlorine-chloride system, electrons flow in the metal from the iodide-iodine system to the chlorine-chloride system. The electrons convert chlorine to chloride, as can be shown by analysis. The electrons escaping from iodide ions leave iodine which can be seen. Change in the proportions of anions to cations on either side is compensated by migration of ions through the bridge, thus completing the circuit.

We speak of half of such a cell as a half-cell. Neither of these half-cells is suitable as a standard.

In figure 3 the half-cell at the left is the standard. Molecules of hydrogen are the proton donors, the donating ability of which is made definite by having the hydrogen at a partial pressure of one atmosphere. Hydrogen ions, which

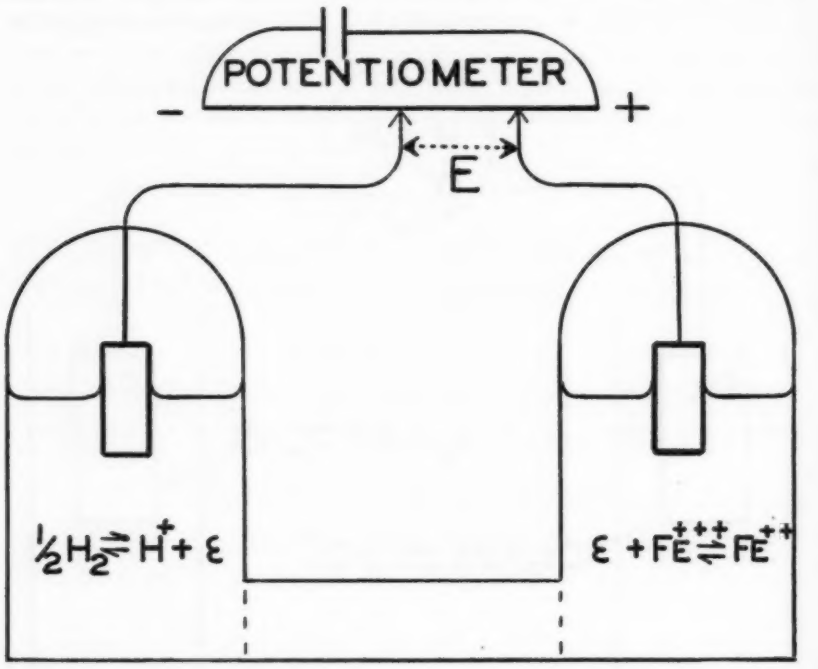


FIG. 3. Hydrogen half-cell joined to a particular half-cell the potentials of which become standardized when hydrogen half-cell is standard. (Diagrammatic.) For the standard the partial pressure of H_2 = 1 atmosphere and pH = 0. See text for comment on junction potential.

in water are hydrated protons, are the electron acceptors. In this standard half-cell they are at that activity commonly designated by pH = 0. A catalyst, such as platinum black, accelerates process (A) to which is coupled the hydration of the proton, process (B).

$$H_2 \rightleftharpoons 2\epsilon + 2H^+ \quad (A); \qquad H^+ + H_2O \rightleftharpoons H^+ \cdot H_2O \quad (B)$$

ϵ represents the electron, H^+ represents the proton, and $H^+ \cdot H_2O$ represents the hydrogen ion of a water solution.

To this standard half-cell one may join any other half-cell. That shown in figure 3 contains salts furnishing ferrous and ferric ions. For present purposes we may omit discussion of the problems associated with the liquid junction and we may assume that an adequately approximate correction for junction potential will have been applied in all cases.

Any such cell is not allowed to operate for then there would be continuous changes of components. Instead, the electromotive force is balanced by that of a potentiometer for two purposes: to obtain the condition of maximal work, which is correlated with the state of the oxidation-reduction system; to measure as an electrical potential the potential factor of the maximal possible energy change. Because the method is comparative, it is convenient to ascribe the measured difference of electrical potential between electrodes to the system under study and to speak of the potential of that system in the given state. This is virtually to assign zero potential to the standard, a convention universally agreed to.

A continuum of proton exchange

If another hydrogen half-cell be joined to the standard, and if the hydrogen pressure be the same in each, the potential is a linear function of what we have come to call the pH of the solution. Now pH was defined originally as the negative logarithm of the hydrogen ion concentration (later as a close approximation of the negative logarithm of the hydrogen ion activity). But what about an alkaline solution with a hydrogen ion concentration of the order of magnitude of 1×10^{-13} equivalent per liter? In such a case one might suppose that so minute a trace of hydrogen ions has little physical significance. Indeed, the potential suppliers of protons may be ten million million times more abundant than hydrogen ions. Accordingly one might well assume that the protons supplied to the hydrogen electrode come directly from proton donors without significant intervention of hydrogen ions. Be that as it may, there is no physical phenomenon showing a sharp demarcation between one extreme where there are abundant proton donors in the form of hydrogen ions (hydrated protons) and the other extreme where there predominate proton donors such as very "weak acids" which bind protons relatively tightly. There is some advantage in the view that a complex system of proton donors and acceptors is a material continuum in the sense that all components are involved in what is substantially one sort of process, exchange of protons. What we call pH is then an indirect measure of the proton escaping tendency of a given system. The more direct measure is the potential of a hydrogen electrode, relative to the selected standard. This potential becomes more negative the stronger the bonding of protons to their acceptors.

A continuum of electron exchange

Virtually the same principle applies when we study any oxidation-reduction system with the electric cell. There is no evidence of free electrons in aqueous solutions. There may be plenty of reductants (electron donors) and plenty of oxidants (electron acceptors). The resultant of the push of the one and the pull of the other will, in favorable cases, produce an electrode potential that is related to the ratio of the concentrations of oxidant and reductant and is characteristic of a system in given state. This potential will be the more negative the greater the escaping tendency of the electrons in the system.

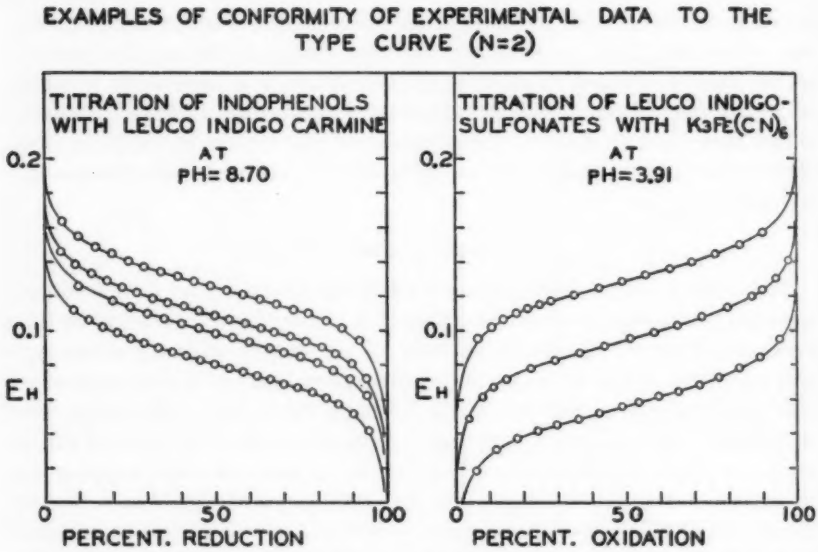


FIG. 4. Curves at constant pH relating electrode potential to per cent reduction (four different indophenols) and relating electrode potential to per cent oxidation (disulfonate, trisulfonate and tetrasulfonate of indigo). Experimental points centers of circles.

Were we dealing with the elegancies of formulation we would recast this in terms of chemical potentials.

To show the precision that may be attained in favorable cases figure 4 is presented. In each of these cases a half-cell containing the substance to be oxidized, or reduced, is connected to the standard half-cell while the reductant, or oxidant, is titrated with a suitable agent. Electrode potential is plotted as ordinate and per cent reduction in one set of cases and per cent oxidation in the other set of cases is plotted as abscissa. The line curves have the theoretical form for the transfer of two electrons. Centers of circles represent experimental data. The conformity is good.

Incorporation of proton exchange with electron exchange

Please note that in each set of cases represented in figure 4 the pH of the solution is specified. The necessity for this appears in figure 5.

In diagram B each sigmoid surve was obtained when methylene white was progressively oxidized to methylene blue. In each case the solution was buf-

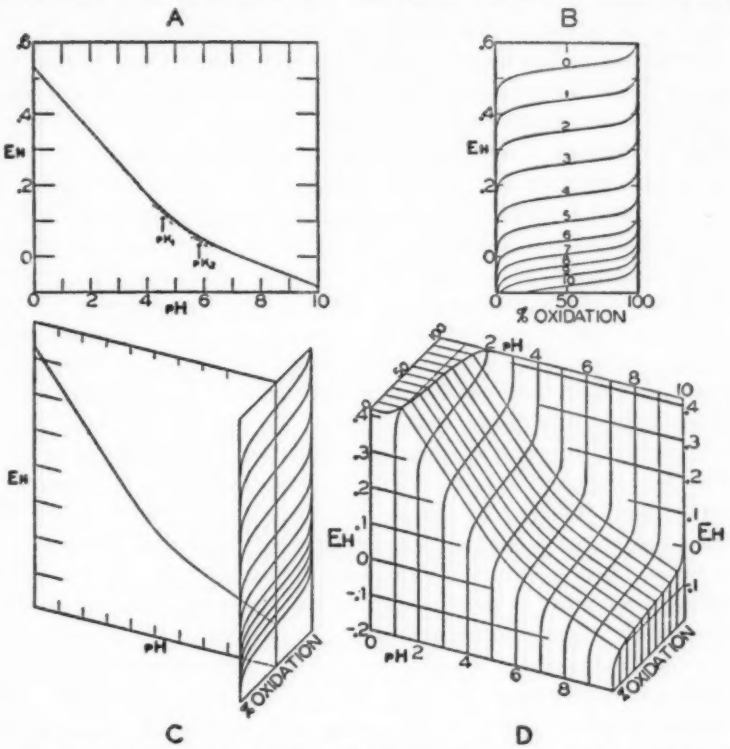


FIG. 5. The methylene blue-methylene white system. A. Relation of electrode potential at 50% reduction (centers of curves B) to pH. B. Relation of electrode potential to per cent oxidation at each level of pH indicated by number on curve. C. Planes of figure A and B mutually perpendicular. D. Isometric drawing of surface on which electrode potential, pH and per cent oxidation are related. Upper plane cuts surface to show curve at constant potential.

fered at the pH indicated by the number on the particular curve. Obviously the position of each curve depends on pH.

In diagram A the mid-points of curves B are plotted against the respective pH numbers.

In diagram C diagram B has been turned in space 90 degrees preparatory

to projecting the sigmoid curves so that their centers will fall on curve A. D is the isometric drawing of the result.

Obviously we have a surface in the 3 dimensions of space; the corresponding parameters being: per cent oxidation, potential as a measure of electron escaping tendency, and pH as a measure of proton escaping tendency.

The pH-effect is simple in principle. The addition of each electron either destroys in the oxidant a place where a proton could have added, or it creates in the reductant a place where a proton may add. Whether and to what extent protons will add depends upon the availability of the protons in the medium and the ionization constants of oxidant and reductant. The pH number of the solution is a measure of the first. Because the ionization constants have unique values in each instance, the pH-effect differs quantitatively from case to case.

In many cases analysis of a reduced, *isolated*, organic compound will show that it contains more hydrogen than the corresponding oxidant. In other cases the oxidant contains more oxygen and some such cases have been treated by a scheme in which the participation of water is invoked and loss of the hydrogen thereof is used to account for the oxidation process. This is no place to debate the merits of this scheme, which may be applicable in some cases. It may be noted that these considerations gave rise to the generalization that oxidation is loss of hydrogen and reduction the gain of hydrogen. Much of enzyme nomenclature stems from this. That this theory cannot be general (and is now recognized to be more or less conventional) may be shown by the following cases. Quinones in alkaline solution may be reduced to the corresponding reductants as ions without acquirement of protons. While two electrons are required to reduce the cation of methylene blue, these are accompanied by one proton, or two protons, or three protons, depending on the pH of the solution which controls ionization. The evidence as it stands today is that in the reduction of a pyridine nucleotide under ordinary conditions two electrons are accompanied by only one proton. These deductions involve knowledge of the structures of the compounds, particularly their electronic configurations, and reasonable allocations of ionization constants to particular groups. In other words there is pooled the information acquired by the organic chemist in his stepwise application of special processes. It also should be noted that for the purpose of reaching a mathematical formulation of the coupling of proton and electron transfers it makes no difference whether one starts with the assumption that only electrons add first and then introduces the equations for ionization equilibria or starts with the assumption that both electrons and protons add together and then introduces the equations for the ionization equilibria, or starts the other way around, provided that, having chosen a point of view, one follows through consistently. This is one way of saying that we cannot tell whether or not these entities are transferred separately, and, if separately, we cannot tell their order. In short, throughout the

argument we use conceptions of distinct processes, whether drawn from the realm of organic chemistry or physical chemistry. The processes are considered to be distinct because they can be made so by selection of systems and conditions. Their distinctness may then be purely conceptual when, as in the cases cited, we find evidence of the intimate coupling of electron and proton transfer.

Such coupling can be illustrated by a simple experiment. Before showing this let me remind you of the color changes that may be observed with the indicator to be used, 2,6-dichlorophenol indophenol. The oxidized form is blue in neutral solution, red in acid solution. The reductant is colorless. Both the color change due to change of pH and the color change due to reduction can be shown while one amuses oneself by comparing the behavior of this dye in real orange juice and in orange-flavored "pop." [During the presentation of the paper the indophenol was added to a locally purchased "pop" labeled to contain various ingredients including "orange." An almost imperceptible reduction occurred; the greater part of the indicator turned red in this acid, carbonated beverage. In contrast, real orange juice reduced to the colorless form all indicator added until, by an accident, the beaker broke!] As is well known, a standard solution of this indicator is used to titrate the ascorbic acid of fruits and vegetables.

Now to the significant experiment. To a liter of water add about 5 grams of potassium ferrocyanide and about 0.2 gram of potassium ferricyanide. This oxidation-reduction system will stabilize the electron escaping tendency. We say it *poises* the potential [compare with *to buffer*]. Add, if necessary, a very little buffer of pH 7 so that the indophenol will be initially in its blue form. Use sufficient indophenol to give the solution a distinct blue color. On careful addition of acid to this mixture one will see the indophenol reduced to its colorless form. This change is reversed on addition of alkali to the acid solution. Reversals can be carried on almost indefinitely. Here one sees changes of pH bring about reversals of the direction of electron transfer between the ferrocyanide-ferricyanide system and the indicator system.

For any specified material change one can calculate an energy change as a singular event and then one will have lost sight of any artificial segregation of two processes.

We may alter the treatment of the quantitative data for this indophenol system to show a relation analogous to a well known relation exhibited by the blood pigment. As the blood pigment is under special conditions so we may choose special conditions for the indophenol. We then calculate that associated with the reduction of one millimole of indophenol there is such a change of ionization that five-tenths of one milliequivalent of cations, previously matched against the anions of the oxidant, would be available to match anions of any kind that we might add in such a way as to keep pH constant. When oxyhemoglobin gives up oxygen to the tissues there is such a change of ioniza-

tion that cations previously matched against the anions of oxyhemoglobin are made available to match incoming bicarbonate ions and to the extent of about five-tenths of one milliequivalent per millimole of blood pigment[1] (minimal molecular weight basis), provided the exchange of bicarbonate anions for protein anions is so perfect that pH remains at 7.4. The opposite effect takes place in the lungs. This phenomenon accounts in large measure for the buffer action of the blood.

There are those who have objected to my drawing this analogy, perhaps because of the very great structural difference between the blood pigment and the indophenol and the difference between a process of oxygenation and one of oxidation. All I say is that in each case a process considered to be distinct from that of the category of acid-base equilibria has caused the same quantitative change in acid-base equilibria. Great structural differences need not obscure a common physicochemical principle.

The counterpart of the change in acid-base equilibria associated with the change of degree of oxygenation of the blood pigment is the shift of the oxygen dissociation curve of oxyhemoglobin with shift of pH. For convenience, and especially for elementary instruction, we plot the two effects separately. In nature the processes are coupled and the energy changes integrated.

Incorporation of coordination phenomena

Now let us consider metalloporphyrins. Figure 6 represents ferroprotoporphyrin IX, commonly called heme, the prosthetic compound of hemoglobin. The "iron" may be converted from the ferrous state to the ferric state by loss of an electron. Although we may be presumptive in allocating the difference of one electron per "iron" to the metal rather than to the metalloporphyrin as a whole, it will suffice for "bookkeeping" to do so. We have used porphyrins other than protoporphyrin and metals other than iron. Attention will be confined to the iron compounds, and, because substitution of one porphyrin for another makes little difference in the relations to be presented, we may neglect these differences.

Figure 7 represents the change of potential (ordinate) related to per cent reduction (abscissa) of ferriprotoporphyrin at a given pH. This is a special example of the sort of relation illustrated by figure 4. Figure 8 represents, on the lower curve, the relation of pH (abscissa) to the potentials, E_h, at midpoints of curves such as that of figure 7. This is a special example of the sort of relation illustrated by diagram A of figure 5. With these last two diagrams one could construct a three dimensional figure such as that of diagram D of figure 5.

The new dimension, the new parameter, is suggested by the upper curve of figure 8. At any given pH and 50% reduction of the system there is a large shift of potential on addition of pyridine. Let us approach stepwise the consideration of this "fourth dimension."

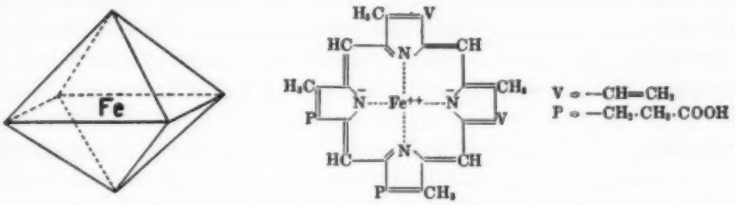


FIG. 6. Fischer's formula of ferroprotoporphyrin IX, often called heme. "Iron" coordinated with 4 pyrryl nitrogens which lie approximately in one plane and may be regarded to be at those four of the apices of the octahedron which lie in the horizontal plane. At the other two of the six apices of the octahedron other "coordinating" substances may be bound.

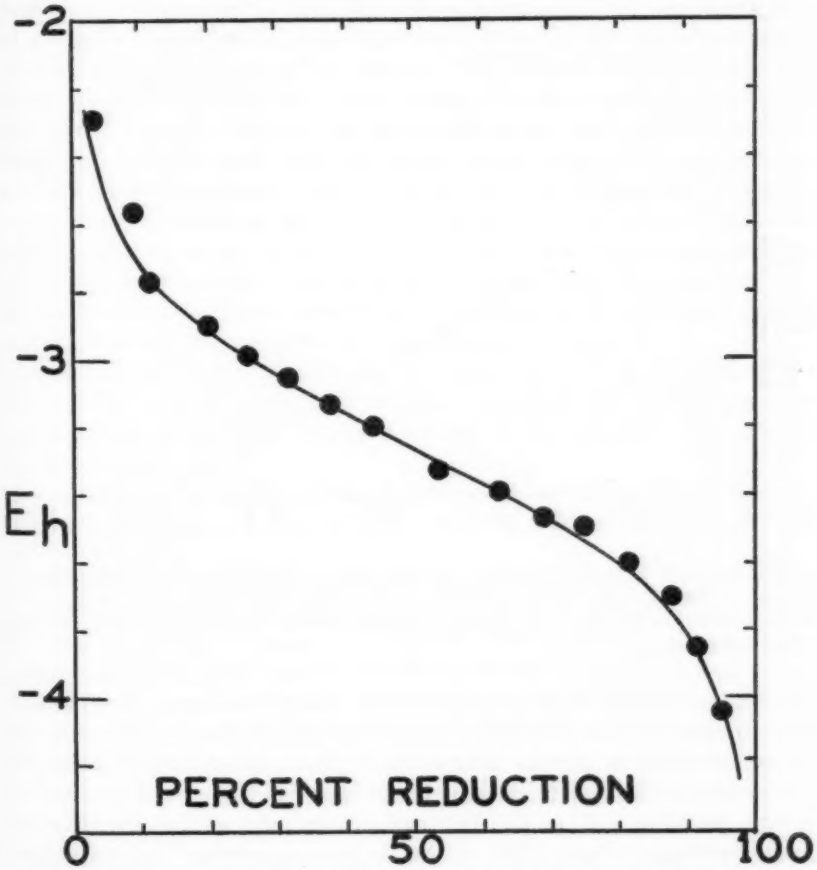


FIG. 7. Relation of electrode potential, E_h, to per cent reduction of ferriprotoporphyrin at constant pH.

The Swiss chemist, Werner, having found that it is impractical to describe ferricyanide and numerous other ions and compounds in terms of the older valence theory, ascribed to iron a "coordination number" which is 6. For present purposes it is unnecessary to account for this in terms of electron orbitals, as can be done. Now in the formula shown in figure 6 the "iron" may be regarded as coordinated with the four nitrogens of the pyrryl rings. There

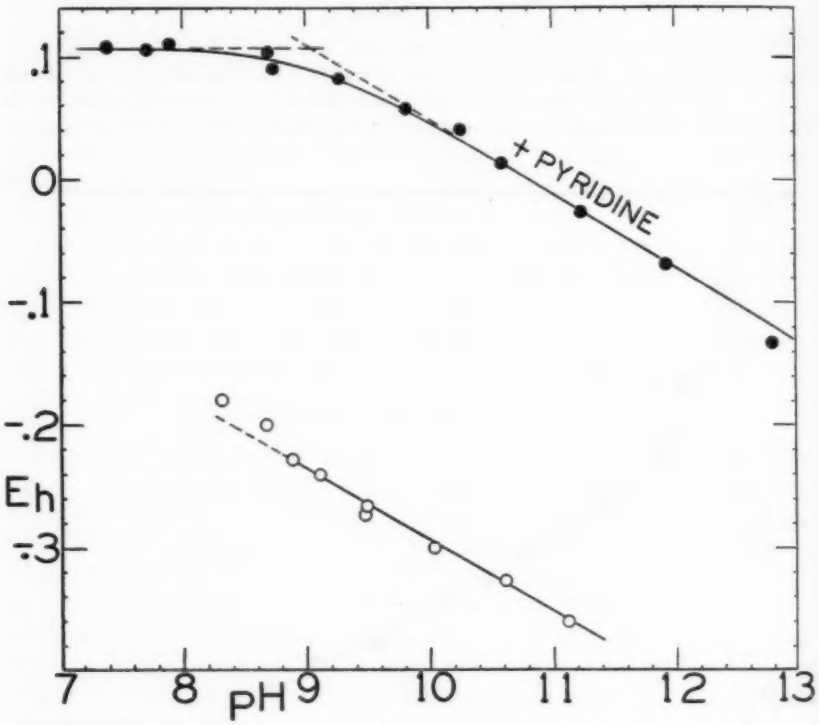


FIG. 8. Lower curve. Heme system. Relation of pH to mid-points of curves comparable to that of figure 7. Upper curve. Relation of pH to mid-points of titration curves of the heme-pyridine system when concentration of pyridine is sufficiently high to saturate both oxidant and reductant.

are left two coordination "places" capable of being occupied. Molecules or ions attached at these places will be above and below the plate-like molecule of metalloporphyrin. Let us assume that in water solution these two places are occupied with water molecules. We have no proof of this. It is a sort of artistic postulate leading to a structural account of a relation for which we have abundant evidence. This is that in alkaline solution the metalloporphyrin in oxidized state has the equivalent of one less proton than the reduc-

tant.* If we follow our "artistic" postulate, a proton has been stripped from a water molecule attached to the oxidized iron but not from one attached to the reduced iron (except at extremely high pH). This is equivalent to adding an hydroxyl ion to the oxidant. One of several evidences is the slope of the lower curve in figure 8.

Now suppose that pH is kept high and constant so that changes of the kind just noted do not occur. Furthermore, let the degree of oxidation be constant. Now add pyridine to the mixture of oxidant and reductant. A rise of potential is associated with increase of the concentration of pyridine. This can be only if the pyridine combines more tightly with the reduced than with the oxidized metalloporphyrin.

We now have 4 parameters and, of course, we cannot diagram the relations within the 3 dimensions of space. We can, however, control all but two factors at a time and examine the relation between these two. Figure 9 shows some significant relations. Here pH is constant. The ordinate is potential, the abscissa per cent reduction. The curve for heme in the absence of pyridine is the second from the bottom. Far above this is the curve marked pyridine heme, the curve obtained when the concentration of pyridine is so high as to saturate both oxidized and reduced heme. The large difference of potential between the mid-points of these two curves is the intensity factor of a *difference* between the free energy of association of pyridine with reduced heme and the free energy of association of pyridine with oxidized heme. The calculated difference is about 33,000 volt-coulombs, or, in terms of the out-dated calorie, about 7,900 defined (as distinct from mean) gram calories.

Analogous is the case of riboflavin. See lowest curve in figure 9. When the oxidized and reduced forms of riboflavin are combined with a particular protein the potentials shift to the curve marked "a flavoprotein". Data are all too few in such cases.

I hesitate to extend the analogy to the methemoglobin and cytochrome *c* systems for reasons that need not now be given. The facts are as illustrated and are suggestive.

The following experiment will show the intimate relation between three processes as the experiment with the indophenol and ferricyanide systems showed the intimate relation between two processes. The experiment with the indophenol and ferricyanide systems can be conducted in the presence of air because neither system is sensitive to oxidation by oxygen. Many other systems are so sensitive to oxygen that extreme care must be taken to remove the last trace of this agent from solutions if complications are to be avoided. The following experiment should be conducted in an atmosphere of pure nitrogen.

* In the region of pH under consideration all the carboxyl groups of the porphyrin are completely ionized so that the ionization here considered pertains to the coordination center.

Select an oxidation-reduction indicator with mid-point potential (center of the sigmoid titration curve at constant pH) half-way between the mid-point potentials of the heme system and the pyridine heme system. Let pH be held constant by means of a buffer. On addition of a little of the indicator to the half-reduced heme system it will be reduced practically completely. Now add

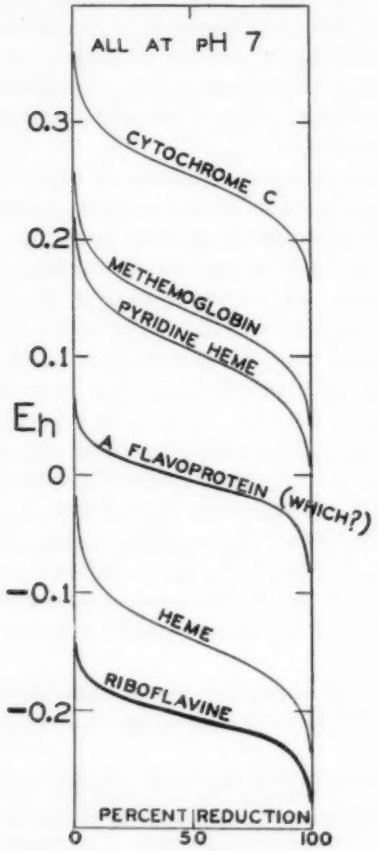


FIG. 9. Titration curves relating electrode potential to per cent reduction at pH 7

pyridine to this mixture. The pyridine combines preferentially with the reduced heme, the potential shifts to a much more positive value, the indicator is practically completely oxidized.

Here we see a neutral substance, which pyridine is in alkaline solution, bring about a reversal of the direction of interaction between two oxidation-reduction systems. A variation of the experiment would be to show that neutral

pyridine causes a change in pH *via* its effect on the heme oxidation-reduction system.

We now have four parameters with which to map relations pertaining to three different processes coupled in one chemical continuum.

I have said that there are four parameters. This is an over-simplification. In experimental work one must keep in mind temperature, ionic strength, possible specific salt effects, in addition to the four parameters mentioned, not to mention the formation of dimers which is discussed later and which necessitates control of the total concentrations of reduced and oxidized metalloporphyrin.

Figure 10 presents too much detail for present purposes. Therefore let us look at the situation as a whole. On the left are curves relating the indirectly measured electrode potentials to per cent reduction of systems involved in metabolism. The curves on the right include a few of the systems that serve as enzymes or as mediators in the metabolism of the systems on the left. To avoid a lengthy discussion I may assert that from the purely thermodynamic point of view the potentials of a particular catalytic system on the right must be in certain relation to the potentials of a particular metabolic system on the left for catalytic efficiency. This, I repeat, is only the purely thermodynamic aspect.

I think you can now sense the possibility that the position of one of the catalytic systems on the right may be greatly altered by the formation of complexes.

At this point it may be well to forestall a question. Someone may ask: Since there is nothing comparable to a metal electrode in a living cell what possible biological applications of potential data can there be?

I assure you that there were no electrodes hidden in the beaker where the indophenol and the ferricyanide systems interacted directly. The outcome of that experiment was predicted by use of measurements made with the electric cell. In the electric cell systems that can act directly on one another either alone or with a catalyst are held apart and electron transport is *via* a metal instead of directly. This permits the measurement of what can take place in the absence of the metal electrodes.

In the last analysis the data being presented are rooted in thermodynamics. There is, however, a very important restriction to thermodynamics. Its data will reveal the possibility that certain postulated reactions can occur and that other postulated reactions cannot occur. Water can run *down* hill; it cannot run *up* hill spontaneously though it may be *pumped* up hill by *input of energy*. Here the orientation of a pressure difference is the determining factor for the spontaneous process. By analogy it is the orientation of a difference in potential that is the determining factor in the oxidation-reduction process. All we can say when we have plotted the potentials of various systems is that

certain reactions between the systems are possible, others are impossible. As we all know, the realization of one of these possibilities often requires a catalyst. Even the hydrogen system, used in the standard of reference, is inactive

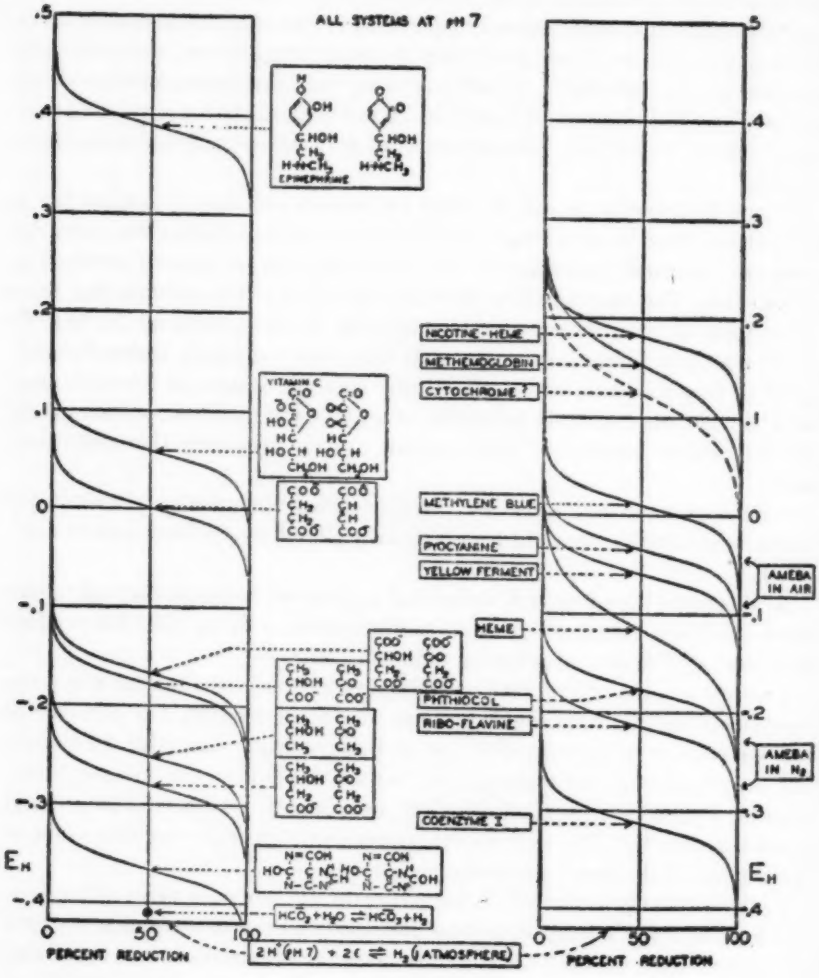


FIG. 10

without a catalyst. The living cell has supplied the enzymes, the special catalysts, for mechanisms regarding which thermodynamics has nothing to say.

There are two cautions, rather than basic restrictions, that should be mentioned. Most of the potential data are for homogeneous systems. We should be cautious in extrapolating to the situation in the living cell where there are phases, phase boundaries and surfaces galore and where, it now appears, some catalysts are virtually in solid phase. Secondly, in a steady state a reductant may be oxidized as fast as it is formed so that it would seem dangerous to apply equilibrium data. The encouraging aspect is that in "reconstructed systems" (those studied with relatively few compounds *in vitro*) many natural processes are found to be reversible. And here, I believe, one easily could be misled if no attention be given to the possible large displacement of potentials incident to the formation of complexes.

To return to metalloporphyrins. We found that we had a bear by the tail and that he was leading us over the bumps in a "fifth dimension" of our contour map. Diffusion coefficients, sedimentation in the ultracentrifuge and other data indicated that heme exists in water solution in aggregates of large and variable sizes. Slight changes of the composition of the solution cause such large changes of diffusion coefficient as to suggest the bonding of the molecules in these aggregates to be weak. Also no evidence of the larger aggregates appears in other data based on energy changes unless it be aggravating, small departures of data from simple theoretical formulations. There does appear in much of the data evidence that the larger aggregates contain units of two molecules, dimers. At least this has proved to be a good postulate in that it has served to rationalize data that could not be well formulated otherwise. It may be, however, that this is the first order approximation of a statistical relation.

I might add that we are not dealing with a unique situation. Many a substance hitherto regarded to be dispersed as molecules in solution is now known to be aggregated in solution.

At any rate, the evidence in this case presented an uncertainty in the use of simple formulations. This was well taken in hand by Dr. Joseph Shack in our laboratory. He undertook to go around a large number of cycles of changes in an effort to establish consistency in formulations. These are a few of the changes: The conversion of oxidized heme to a complex (with pyridine, or $\overline{CN}$), first in alkaline solution then in neutral solution; similar conversions of the reduced heme; the conversion of reduced to oxidized heme and of the reduced complex to the oxidized complex, first in alkaline solution, then in neutral solution; the pH effects studied independently, etc., etc. Each case was studied as a series of equilibrium states. All this required the mathematical formulation of various possible postulates. We sought first the best correspondence between fact and formulation in each case and gave the greater weight to the more critical tests. Finally there must be consistency of formulation on completion of all cycles of change. Frequently one is frustrated by

the properties of these stubborn systems, particularly the very low solubilities of components.

Here we are dealing with special detail, not particularly important to the theme of this review, detail that one is obligated to obtain in order to leave a clear, clean record and to avoid the charge that one is a "cream skimmer".

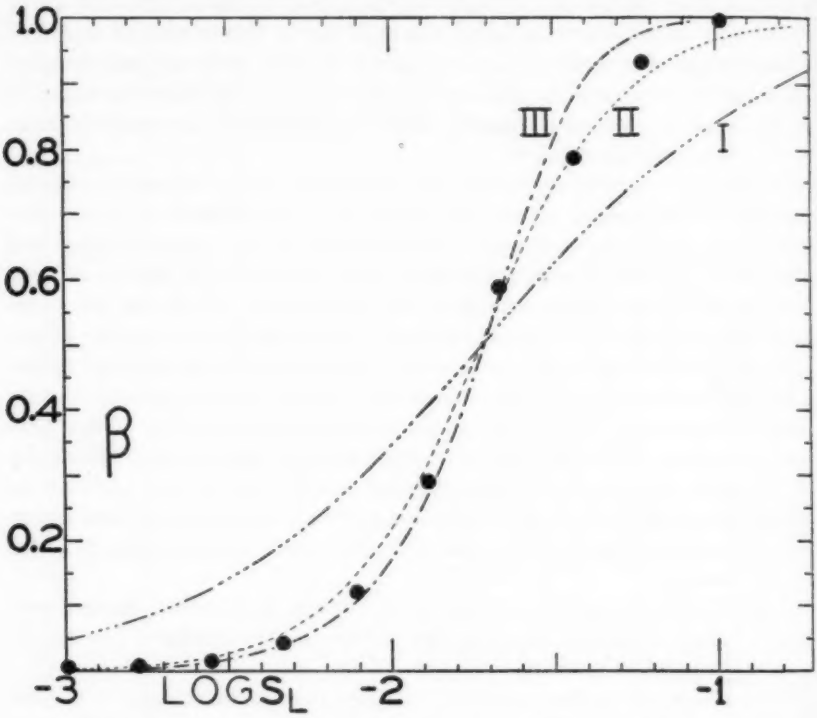


FIG. 11. ● Experimental points relating degree, β, of transformation of ferrimesoporphyrin to the complex containing 4-CH_2OH-imidazole to the logarithm of the total concentration, S_L, of this ligand.

Curve I: theoretical for $M + L \rightleftharpoons ML$
Curve II: theoretical for $M + 2L \rightleftharpoons ML_2$
Curve III: theoretical for $M_2 + 4L \rightleftharpoons 2ML_2$

In passing I may remark that the studies constitute a beautiful case in which respectable data are open to various interpretations and in which certain limitations of experimental methods are clearly revealed.

A few items from recent work conducted by Robert Cowgill will suggest part of what we have to deal with.

Figure 11 represents a case in which constant concentration of ferrimeso-

porphyrin was used with increasing concentrations of a particular imidazole. The logarithm of the concentration of the imidazole is plotted as abscissa and the degree, β, of conversion to the complex, as determined spectrophotometrically, is plotted as ordinate. Three curves represent three different hypotheses regarding the process by which the complex is formed. Obviously the simplest postulate represented by curve no. I does not apply. To make short a long story, we can present arguments for and against postulates made to account for the departure of the data from either curve II or curve III. Please bear in mind that we have a system which presents various possible complications. I could show other data which fit the contour of curve II so well that we might

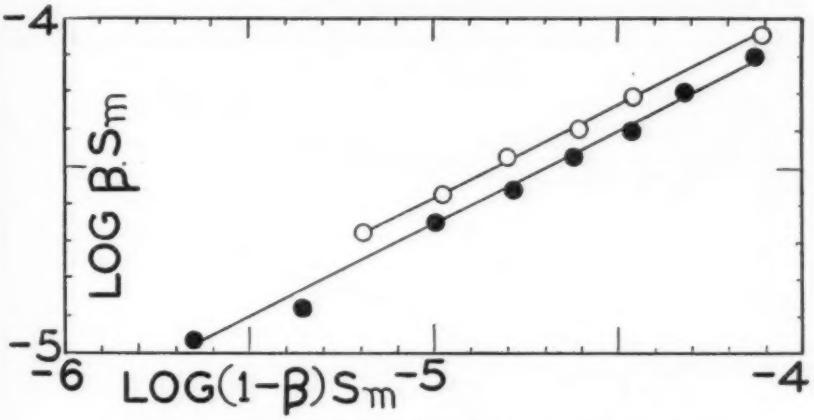


FIG. 12. Test of relation III (see legend of figure 11) by "dilution test"
○ Pilocarpine ● Histidine

easily have been led to the conclusion that the postulated process on which curve II is based is the real process.

Fortunately we have a critical test to which we must give the greater weight. By measuring the degree of transformation to the complex at different dilutions of the metalloporphyrin but constant concentration of coordinating substance and plotting the functions shown in figure 12 we should get a straight line with *no* slope if the process goes one way and a straight line with the slope shown if the process goes in another way. Figure 12 shows that the data fit best the straight line with the slope shown.

From these experiments we deduce the following. (1) The final product contains two molecules of imidazole per iron atom. (2) This is attained by addition of four molecules of imidazole to the dimeric metalloporphyrin accompanied by the splitting of the dimer. (3) Although the process doubtless is complicated in its kinetics and although intermediates doubtless are formed,

the intermediates must be very unstable. If they persisted at the equilibrium state, the curve in the experiment represented in figure 11 would be elongated and if there were present a large proportion of an intermediate the curve would be in steps comparable to steps observed in the titration of a complex acid. Possibly the departure of the data from curve III (fig. 11), which expresses the postulate adopted, may be due to the presence of an intermediate in a small proportion, but this cannot be proved because of the limitation of the experimental method.

The evidence is that the first imidazole adds with more difficulty than the second. An analogy is found in the oxygenation of hemoglobin. The first oxygen adds with more difficulty than the second.

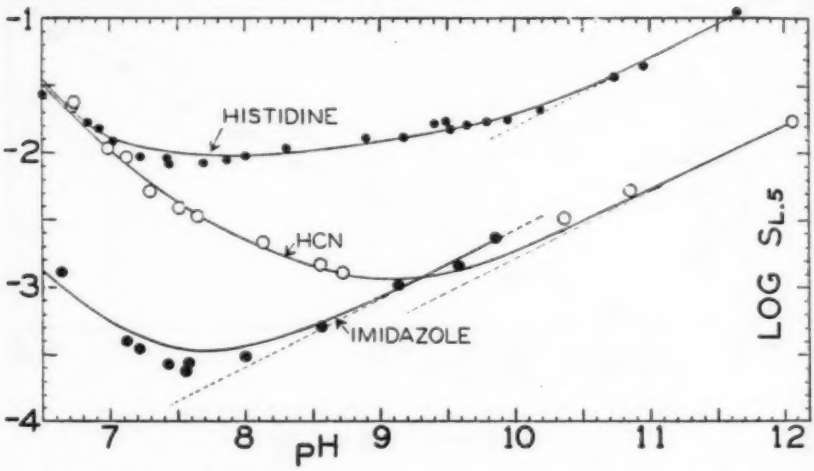


FIG. 13. Relation of pH to logarithm of that concentration of ligand $S_{L.5}$ required to half saturate ferrimesoporphyrin.

Now let us look at one aspect of what may be called competition between a ligand and hydroxyl ion for position in the coordination shell of the metalloporphyrin.

Each curve in figure 13 was obtained under the following conditions: constant concentration of metalloporphyrin in oxidized state; each value of log $S_{L.5}$ is the logarithm of that concentration of ligand at which half of the metalloporphyrin is converted to the complex. In each case the unbroken line was calculated with experimentally determined constants that cannot be evaluated with the highest precision because of the low solubility of the metalloporphyrin, dimerization, etc.

The upturn of each curve at low pH means that an imidazole (two cases among several are shown) does not combine with the metalloporphyrin when

the ring nitrogen acquires a proton. Likewise HCN does not combine; only the cyanide ion combines with oxidized metalloporphyrin. The minimum of each curve is determined in part by the ionization constant of the ligand and in part by the ionization constant pertaining to the hydroxyl group coordinated with each "iron". Because the ionization constants of the ligands are distinct, the minima are different. The apparent pK_a' of hydrocyanic acid is about 9.1 while that of imidazole under the conditions used is about 6.9; hence the minimum for the cyanide case is at much the higher pH.

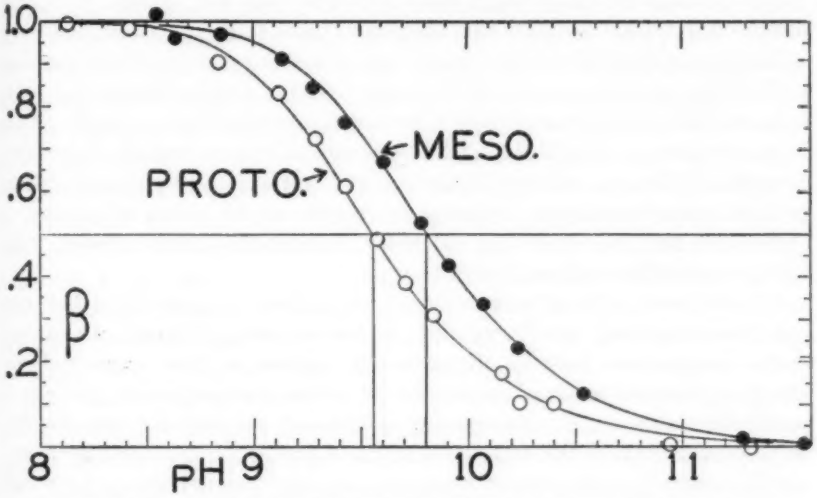


FIG. 14. Relation of pH to degree of saturation (β) of ferriprotoporphyrin and ferrimesoporphyrin with pilocarpine.

In the region of pH much greater than the value of pK_a' there is an upturn of each curve and the distinct slope shown. These features are due to competition between ligand and hydroxyl ion for position in the coordination shell of the "iron".

This competition can be shown neatly by a little trick. One chooses such a concentration of an imidazole (hydrolyzed pilocarpine in this case) and such a concentration of metalloporphyrin that no appreciable combination occurs at high pH (high hydroxyl ion activity) while practically complete combination will occur near pH 8. On introducing this fixed mixture into buffers of different pH values and measuring the degree of combination (ordinate) one obtains the data shown in figure 14 by points. The data conform to the theoretical curve. One curve is for the system containing ferri*meso*porphyrin, the other for the system containing ferri*proto*porphyrin.

These curves are so like those for the ionization of an acid that one easily

could be misled. The equilibrium constant is not an ionization constant; it is a catch-all constant involving three different constants, each pertaining to a particular process. In other words we have here the resultant of the coupling of processes.

Returning to the case of the cyanide ion as ligand I might mention a remarkable phenomenon. On adding a mixture of cyanide and pyridine to an oxidized metalloporphyrin one might expect to find a mixture of the dicyanid- and the dipyridine complexes and the proportions of each that could be calculated from the respective equilibrium constants. This does not happen. If, under suitable conditions, one adds to a solution of heme so little cyanide that only a little of the cyanide complex forms, and to an aliquot of the heme solution so little pyridine that only a little of the pyridine complex forms and then mixes the solutions, presto—there is formed an abundance of a complex. This is spectrophotometrically distinct from the dicyanide and from the dipyridine complexes. This and other evidence indicate that it is a monocyanid-monopyridine metalloporphyrin. I suppose one might call this a case of synergy.

Again in this case there is a pH effect comparable to those shown, indicating competition against hydroxyl ions.

I have shown a few of many cases in which there is competition between ligand and hydroxyl ion for position in the complex. Although we cannot make a comparison between the structural features in these cases and the structural features involved in the case of alcohol dehydrogenase, there is a parallelism to this extent: As reported by Theorell, the ratio between the dissociation constants of the *oxidized* coenzyme-I protein complex and the dissociation constant of the *reduced* coenzyme I-protein complex varies from 200 at pH 7 to 1 at pH 10. In other words, there is some sort of competition comparable *in principle* to that illustrated in our model system.

A by-product of the investigations made with imidazoles is the following. There is current a hypothesis that the points of attachment of heme to the protein globin in hemoglobin are the imidazole rings of histidine residues. Now none of the simple imidazoles, including histidine, which we have studied binds to any iron porphyrin, oxidized or reduced, with the firmness that we infer of the bonding of iron protoporphyrin in the blood pigment or its derivatives. We can say that while our data make no *positive* contributions to the still unsolved problem of how heme is bonded to globin, a postulate made without knowledge of our quantitative data for simple imidazoles might be too naïve.

A note on phosphorylation

For the complete description of any one of our model systems we have to use at least four parameters. Since reference has been made to analogies in the field of enzyme chemistry it may be appropriate to mention a parameter,

or set of parameters, now uppermost in the minds of enzymologists. It would hardly do to omit mention of phosphorylation and transphosphorylation.

The developments in this field are, perhaps, the most brilliant in the history of biochemistry. Many regard the subject to be the key subject of metabolism. In a few of those cases in which a process of phosphorylation is coupled with the oxidation-reduction process there are data that can be incorporated in contour maps such as those presented here. Unfortunately much of the data being copied in treatise after treatise are crude estimates made by devious calculations. In part this is due to the inherent difficulties of a more direct attack; in part this is due to the compelling urge to have the estimates whatever their reliability. Furthermore, some of the estimates are ambiguous and some are wrongly labeled. Ambiguous are those statements that fail to specify the ionizations of components. Erroneously labeled are data on so-called high-energy phosphate bonds, which some of us, referring to the symbol used, call P $\sim$ wiggle. This is not a bond energy as bond energy is known in chemistry. An energy datum commonly called phosphate bond energy is the energy of hydrolysis. When such an energy is very high it cannot be measured by equilibrium studies because at equilibrium there is left too little unhydrolyzed substance to measure. It seems inappropriate to emphasize a quantity before its experimental evaluation can be given equal emphasis. Nor does it seem necessary to adopt this way of going about the matter.

When the extremely brilliant work on isolation of components, on mechanisms and on kinetics shall have advanced to the point where new approaches to the thermodynamic problem are revealed and it becomes possible to design experiments for accurate measurements of free energy changes in phosphorylation and transphosphorylation we shall have contour maps (piecemeal of course) in at least five dimensions.

A note on a cross connection with hydrolysis

I cannot refrain from mentioning a very special sort of cross-connection between oxidation-reduction and hydrolysis. The best documented case is the hydrolysis of urea as accelerated by the enzyme urease. Dr. Hellerman showed beyond reasonable doubt that the activity of this enzyme is dependent upon the preservation of certain of its sulfhydryl groups. If these are blocked by a substituent, or if the —SH is oxidized to —S—S, activity ceases. Reduction of the —S—S— to —SH restores activity.

DISCUSSION

If we now recall that we were led to study the metalloporphyrin-ligand system by reflection on a problem presented by the early knowledge of those enzyme systems which are composed of "prosthetic" and "ligand" parts, it will be asked why we have not made use of natural systems now available.

Are we not "off the beam"? We have done enough with one natural system to appreciate both the inherent difficulties in handling it and the probability that we might have been far off the beam had we not had experience with the artificial, model system. We think it important to distinguish structural features from such common physicochemical relations as there may be. The structural features of components of most natural systems differ very greatly from those of components of our artificial system. There may also be great differences in the nature of bondings. It remains to be seen how far we are "off the beam." I have faith that our little beam will serve as a direction finder in local flights at least. Be that as it may, there remains a picture of a concrete chemical continuum that may be briefly summarized as follows.

(1) The hydrogen electrode responds to the escaping tendency of protons wherever found. There is no physical phenomenon that shows a sharp demarcation between the withdrawal of protons from hydrogen ions (hydrated protons) and from other proton donors although it is convenient to resolve the free energy change in a hydrogen cell into free energy of ionization of an acid, for example, and free energy of hydrogen ion dilution. In other words, all sorts of proton donors and their conjugate acceptors form an "acid-base" continuum.

(2) In the reduction of many an organic compound conditions may be found under which only electrons are concerned but a change of conditions brings about the participation of protons and when this occurs segregation of the two sorts of process is artificial. In a complex system containing many potential oxidants and reductants there is an oxidation-reduction-acid-base continuum involving inseparable electron and proton transfers, not to mention incorporation of oxygen.

(3) There are many known cases in which an oxidant, or a reductant, or both, combine with another sort of substance. I have sketched briefly data on some concrete cases. Here are blended the processes of coordination, of exchange of electrons and of exchange of protons.

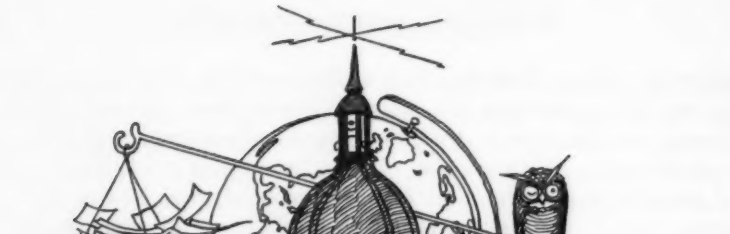
One can envisage innumerable paths in shifts of equilibria in such cases. By control of conditions the chemist can make the path a zig-zag path, each zig or zag being parallel to one of his chosen parameters. But is any such a path followed in nature? Of course, if one were to investigate a natural system by using in turn methods that reveal first a change of pH, second a change of potential, etc., etc., his description might well be in terms of the zigs and the zags. However, this would be no answer to the question. The question may be put in another way. Does a living cell follow the chemist's parameters? So beautiful are some of the known cases of harmonious interrelations from which it is impossible to pick a controlling factor that one is led to suspect an underlying common phenomenon. In terms that are too general one can now say that all chemical processes have in common the

transition of "valence electrons" from orbital to orbital. This is an invaluable *concept* reached by pooling a vast amount of information. But to invoke it in the present instance is to be both too general and somewhat irritating; and for a simple reason. Our assemblies of quantitative data must be built up by use of available experimental methods and none of these escapes from the restriction that it deals with a particular resultant of the common process. Thus, as we look at the matter from the point of view of the experimentalist, we appreciate how much remains to be done with methods that can give us nothing but the zigs and the zags with which we construct contour maps in many dimensions. But having even a limited number of such maps we are less likely to look to one parameter as having outstanding importance or exclusive control in natural processes. For example, we have passed the day when control of respiration was attributed exclusively to blood pH or exclusively to the partial pressure of CO_2. Even the modern multiple factor theory is weak in that descriptions have too much special zig and zag and involve too little knowledge of the chemistry of nerve centers.

As L. J. Henderson remarked in his Silliman Lectures on blood, there is "a physico-chemical integration of the organism which seems to be more primitive than any other form of integration." I take it that by *primitive* he meant primordial.

My good friend and wise counselor, Dr. Cohen, suggests that the final stroke in this rough sketch be a bold arrow pointing to the large number of different processes detected in living organisms. One can imagine the humble amoeba, if it had an intelligence, to be amused by a chemical continuum depicted with only four or five parameters. The humble amoeba must be using many processes in its own still mysterious way and I doubt that it does so by following zigs and zags parallel to the chemist's parameters. Thinking thus, as I reviewed our little contributions, I dreamed that:

I once met a lively young cell
Whom I then proceeded to tell
Of pH, electrons,
P ~ wiggles, protons;
To which he replied: "Go to ——."



BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

Rosenau's Preventive Medicine and Hygiene, 7th edition. By KENNETH F. MAXCY. 1462 pp., $14.00. *Appleton-Century-Crofts, New York.*

The appearance of a new edition of "Rosenau" is very welcome to every worker in any of the many fields of public health. Since the first appearance of the volume in 1913 it has been the indispensable companion of health officers and their varied co-workers. Now after a lapse of sixteen years Dr. Maxcy and a distinguished list of co-workers have rewritten this unique volume and restored it to its former usefulness.

The newcomer to public health will find the broad picture of the subject it presents invaluable to his orientation. The experienced practitioner can again make himself at once familiar with the state of affairs in any of the many special fields into which modern public health is now divided.

The new volume differs from the old in many important respects. The increasing complexity of public health in theory and practice makes it impossible for any single individual to cover more than a small part of the subject and the collaboration of many individuals is essential to any comprehensive treatment. Dr. Maxcy has, however, cemented the contributions of those who have written the special sections of the new volume into a most satisfactory unity.

The expansion and changes in our knowledge are reflected in the changing emphasis of the different sections. Communicable Disease still, of course, occupies much space but the discussion is concerned less with the familiar bacterial diseases than with those new infectious agents which now play so important a part in the communicable disease picture. Nutrition, Medical Care and Infant Welfare are allotted much more space than in previous volumes. Of particular excellence are the sections on Environmental Hygiene, Industrial Hygiene, Diseases of Occupation and Methodology, especially the article concerned with Statistical Reasoning.

The new volume must be regarded as an absolutely necessary occupant of the shelves of the libraries of health departments and schools of public health.

A. W. FREEMAN

Kreislaufuntersuchungen am Menschen mit Fortlaufend Registrierenden Methoden. (Examination of the Circulation of Man with Continuous Registration Method). By K. MATTHES. 326 pp., Ganzleinen DM 48. *Georg Thieme Verlag, Stuttgart, Germany.*

No one is better qualified to discuss the subject of circulatory studies by means of photoelectric methods than Matthes, who is now Professor of Medicine at the University in Erlangen, Germany. Matthes was the first to measure oxygen saturation in blood by photoelectric methods, using simultaneous measurements of light absorption through the red and green part of the spectrum. He also first used the transmission of light through the ear to determine the oxygen saturation of arterial blood.

The purpose of the monograph of Matthes is, to use his own words, "A description of photoelectric registration methods in man." These methods consist in photoelectric kymography, photoelectric registration of the oxygen saturation of blood (oximetry), the continuous registration of blood pressure, and the registration of pulse frequency.

In his chapter on photoelectric kymography, the author makes use of the fact that "fluctuation in the transmission of light reflects changes in the blood content of an organ." In order to obtain changes in the volume of blood perfusing an organ, Matthes uses transillumination with white light with a photocell which is sensitive only in the infra-red portion of the spectrum. This permits the measurement of volume changes in the fingers and the recording of pulsations of blood vessels in the skin.

The theoretical foundation of the determinations of oxygen saturation of blood by means of photoelectric registrations are discussed in great detail. It is of interest that Matthes first suggested arterialization of the ear by means of histamine. For the determination of skin temperature, the author describes the more conventional methods (thermocouples). He believes that skin temperature determinations are of importance especially when performed in conjunction with measurement of the oxygen saturation and volume determinations.

After a description of various photoelectric methods, the author proceeds to investigate in detail the influence of respiration and of arterial occlusion on the oxygen saturation of the blood and on vascular reactivity. He discusses the effect of vasodilators, changes in temperature, and of peripheral vascular disease on "volume pulsations." Subsequent chapters deal with the influence of respiration on peripheral pressures and on pulse frequency.

This book represents probably the most thorough description of the use of photoelectric methods in the physiology of respiration and circulation in man. It is not easy to read, even for those familiar with the German language. The style is sometimes confusing and involved, a common finding in the German scientific literature. Another factor which makes the book difficult to read is the complexity of some of the illustrations; for instance, on a small strip of paper, more than nine different physiological events are recorded.

This book must be considered as one of the great standard works in the use of photoelectric methods in physiology and medicine. It is hoped that an English translation will be soon available to bring this valuable material within reach of the English and American physiologist and clinical investigator.

RICHARD J. BING

Atlas der Pathologischen Anatomie. By R. RÖSSLE AND K. APITZ. 298 pp., Ganzleinen DM 87. *Georg Thieme Verlag, Stuttgart, Germany.*

This atlas, containing reproductions which for the most part are in color, is arranged on an anatomical basis: heart, pericardium, blood vessels, bone marrow, lymph nodes, spleen, etc. All of the photographs deal with gross material. As is usual with colored reproductions of gross organs one is plagued with highlights. The commoner lesions are adequately covered

though as is usual with such an arrangement one does not gain any coherent picture of a given disease. There is a short descriptive text dealing with the lesions which are illustrated With a few exceptions the illustrations contained in this atlas add little to those which may be found in the usual textbook of pathology. One is impressed again how little color reproduction adds to a good black and white photograph.

R. H. F., Jr.

Clinical Methods, 12th edition. By Sir ROBERT HUTCHISON AND DONALD HUNTER. 484 pp., $5.00. *J. B. Lippincott Co., Philadelphia, Pa.*

This is the twelfth edition of this elementary textbook, the aim of which is to describe "those methods of clinical investigation, by the proper application of which a correct diagnosis can alone be arrived at." An introductory chapter outlines the authors' technique of history-taking and physical examination. The rest of the book is occupied with a system-by-system description of physical and laboratory diagnostic methods. One is struck by the extraordinary conciseness which makes it possible to cover so many topics in so few pages. It is likely, however, that this book will have only a limited usefulness for American medical students. Paradoxically, the authors give the impression that systematic thoroughness is not needed for careful diagnosis. For example, in taking a history, one need review symptoms related to the various organ systems only as they pertain to the patient's particular illness. Rectal examinations are to be done only "if necessary," and, discreetly, no mention is made of pelvic examination.

A great portion of the book is spent in descriptions of laboratory techniques. In general, these are accurate, but for the most part, they are too brief to serve as a practical guide. The format of the book is excellent, and there are a number of interesting photographs illustrating various disease entities.

O. D. R.

Rehabilitation Nursing. By ALICE B. MORRISSEY. 299 pp., $5.00. *G. P. Putnam's Sons, New York.*

Miss Morrissey has written a clear and comprehensive reference book on the modern concept of rehabilitation in practice as well as in theory. It is written primarily for the graduate and student nurse but there is much material of interest and value to members of the adjunct professions of physical therapy, occupational therapy and speech therapy; and to allied workers in social service, vocational guidance and recreation.

In addition to the techniques of nursing care of the chronically handicapped, the importance of motivation and the development of self-care activities have been stressed. Photographs and diagrams have been chosen for clarity and interest, the text material is well organized and logically presented. No less valuable is the author's own philosophy of rehabilitation as a responsibility to be assumed by layman and professional alike.

M. E. M.

Antibiotic Therapy. By HENRY WELCH AND CHARLES N. LEWIS, with a foreword by Chester S. Keefer. 562 pp., $10.00. *The Arundel Press, Inc., Washington, D. C.*

The advertiser's blurb says that this book is "a clinical desk guide for the rational use of all antibiotics in all susceptible diseases." As far as this reviewer can tell, this also was the goal of the two authors who are members of the Division of Antibiotics of the Food and Drug Administration. This goal is not attained.

For instance, the first antibiotic discussed in detail is tyrothrycin, which to date has little rational use in therapy. Then the diagrams on the sensitivity of various organisms to

penicillin, streptomycin, etc. simply do not give any information on pneumococci or staphylococci. That is found buried somewhere in the text.

The desire not to be critical of anything that has been passed for marketing on the unsuspecting public is well illustrated by the statement concerning certain tablets containing streptomycin, polymyxin and bacitracin. "These tablets have been used with some success in amebic dysentery, ulcerative colitis and a number of so-called undiagnosed diarrhoeas."

Thus this book is a summary, with little constructive criticism, of the variety of products that are now given to patients whenever they have a fever or might have an infection. It follows the popular practice of giving "broad spectrum antibiotics" whenever you don't know what else to do. We still need a "clinical desk guide for the rational use of all antibiotics in all susceptible diseases."

F. B. B.

BOOKS RECEIVED FOR REVIEW

Adrenal Cortex. Transactions of the Second Conference, November 16–17, 1950, New York. Edited by ELAINE P. RALLI. 209 pp., $3.00. *Josiah Macy, Jr. Foundation, New York.*

Annual Report on Stress. By HANS SELYE. 511 pp., $10.00. *Acta Inc., Montreal, Quebec, Canada.*

Aphorisms of C. H. Mayo and William J. Mayo. Collected by FREDERICK A. WILLIUS. 109 pp., $2.75. *Charles C Thomas, Springfield, Illinois.*

The Battle for Mental Health. By JAMES CLARK MOLONEY. 105 pp., $3.50. *Philosophical Library,* New York.

Differential-Diagnostische Symptomatologie. By W. CATEL. 640 pp., Ganzleinen DM 69. *Georg Thieme Verlag, Stuttgart, Germany.*

Factors Regulating Blood Pressure. Transactions of the Fifth Conference, February 15–16, 1951, New York. Edited by BENJAMIN W. ZWEIFACH AND EPHRAIM SHORR. 238 pp., $3.75. *Josiah Macy, Jr. Foundation, New York.*

An Introduction to Materia Medica and Pharmacology, 6th edition. By ELSIE E. KRUG AND HUGH ALISTER MCGUIGAN. 612 pp., $4.25. *The C. V. Mosby Co., St. Louis, Missouri.*

Liver Injury. Transactions of the Ninth Conference, April 27–28, 1950, New York. Edited by F. W. HOFFBAUER. 232 pp., $3.00. *Josiah Macy, Jr. Foundation, New York.*

Medical Milestones. By HENRY J. L. MARRIOTT. Foreword by Sir Alexander Fleming. 293 pp., $3.50. *The Williams & Wilkins Co., Baltimore, Md.*

Nerve Impulse. Transactions of the Second Conference, March 1–2, 1951, New York. Edited by DAVID NACHMANSOHN. 204 pp., $3.50. *Josiah Macy, Jr. Foundation, New York.*

The Pathogenesis of Tuberculosis, 2nd edition. By ARNOLD R. RICH. 1018 pp., $15.00. *Charles C Thomas, Springfield, Illinois.*

Penicillin Decade, 1941–1951. By LAWRENCE W. SMITH AND ANN D. WALKER. 122 pp., $2.50. *Arundel Press, Washington, D. C.*

Pharmacopoea Internationalis, 1st edition. Vol. 1. 406 pp., $5.00. *World Health Organization, Geneva, Switzerland.*

Problems of Aging. Transactions of the Thirteenth Conference, February 5–6, 1951, New York. Edited by NATHAN W. SHOCK. 194 pp., $4.00. *Josiah Macy, Jr. Foundation, New York.*

Renal Function. Transactions of the Second Conference, October 19–20, 1950. Edited by STANLEY E. BRADLEY. 178 pp., $3.00. *Josiah Macy, Jr. Foundation, New York.*

Report of the Medical Research Council for the Years 1948–1950. Presented by the LORD PRESIDENT OF THE COUNCIL TO PARLIAMENT by Command of His Majesty, July 1951. 247 pp., 6s. 6d. net. *His Majesty's Stationery Office, London, England.*

A Study of Antimetabolites. By D. W. WOOLLEY. 269 pp., $5.00. *John Wiley & Sons, New York.*

Surgery of the Oblique Muscles of the Eye. By WALTER H. FINK. 350 pp., $8.75. *The C. V. Mosby Co., St. Louis, Missouri.*

A Translation of Galen's Hygiene. By ROBERT MONTRAVILLE GREEN. With an Introduction by Henry E. Sigerist. 277 pp., $5.75. *Charles C Thomas, Springfield, Illinois.*